INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL

Qualification of Excipients for Use in Pharmaceuticals

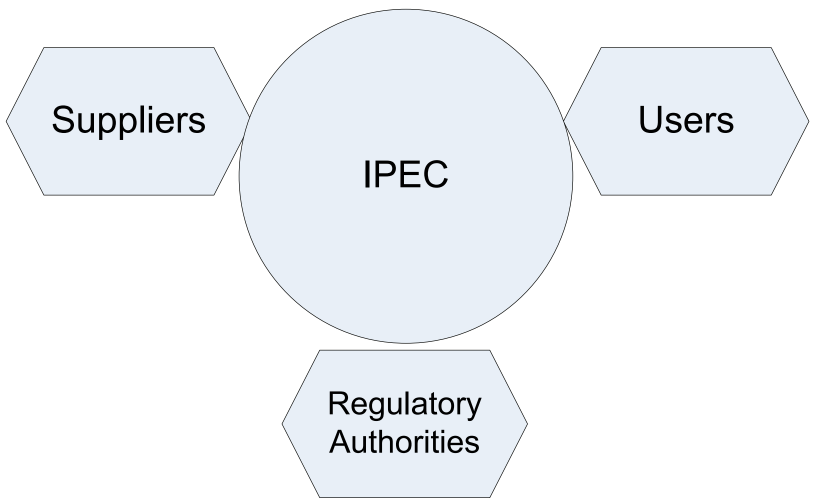
QUALIFICATION OF EXCIPIENTS FOR USE IN PHARMACEUTICALS

FOREWORD

IPEC is an international industry association formed in 1991 by manufacturers and users of excipients. It is an association comprising three regional pharmaceutical excipient industry associations covering the United States, Europe, and Japan (which are known respectively as IPEC-Americas, IPEC Europe, and JPEC). IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace and the development of best practice and guidance concerning excipients.

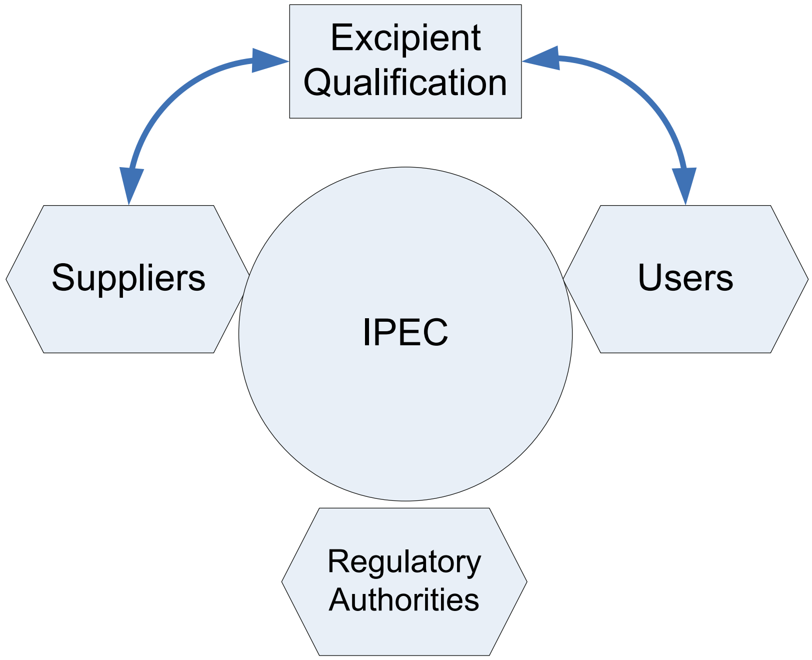
IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, who are considered suppliers in this document,
2. Pharmaceutical manufacturers, who are called users, and
3. Regulatory authorities who regulate medicines.



This document offers best practice and guidance in the establishment of an effective relationship between an excipient supplier and excipient users. The excipient supplier may be a manufacturer or a distributor (or both). It concentrates on the issues that the two parties are likely to encounter and offers advice and best practice as to how to address them, thereby ensuring a smoother relationship and easier use of the excipient by the user and in their dealings with the regulatory authorities.

Because excipients are diverse and often have uses other than in pharmaceutical applications, a supplier may discover that their product is being used by the pharmaceutical industry as an excipient. This document will be especially valuable in such situations because many of the issues described will be new to the supplier.



Thus any material used in the pharmaceutical drug product will be required to be manufactured under appropriate Good Manufacturing Practices (GMP) and supplied under Good Distribution Practices (GDP). The exact definition of GMP or GDP will depend on the material in question (e.g. excipient, active pharmaceutical ingredient, packaging etc) and legislation where the excipient is supplied or sold. Within this guide the terms GMP and GDP are used to encompass all of these various definitions.

Like all guides this document is not meant to be proscriptive, and suppliers and users may follow the guideline as written or find their own manner to address the subjects highlighted. The guide is intended to be comprehensive and covers the essential aspects of the supplier-user relationship. In this regard not every topic may be appropriate for all relationships.

To facilitate reading, the excipient qualification process has been presented in flow charts as a means of linking the activities and steps in a logical manner. This aids comprehension and places these steps into context.

There is no specific requirement to follow the exact sequences of actions as detailed in the flowcharts although users will find these helpful to ensure all aspects are considered.

Although excipient qualification does not directly involve the regulatory authorities, they set many of the conditions that have to be satisfied if a user is to employ an excipient in their medicine.

This document describes the three phases of the excipient qualification process. The layout and content are as follows:

Section 1	Introduction: describes the scope, purpose, and layout of this guide.
Phase 1	**The Excipient Supplier's Process**
Section 2	General Guidance: provides background concerning excipient manufacture, regulation, and controls.
Section 3	Excipient Development and Specification Process: provides guidance to excipient suppliers on the development of an excipient and its specifications.
Phase 2	**The User's Process**

Section 4	Excipient User Assessment, Selection, and Specification Process: provides guidance on how users should assess the excipients for inclusion in their formulations.
Phase 3	**The Negotiation Process**
Section 5	Excipient Supplier-User Negotiation Process: provides guidance on the development of an agreement between the excipient supplier and pharmaceutical user to define excipient quality requirements.
Glossary	Terms defined in the glossary appear in **bold** the first time they are used in this document.
Appendices	Flow diagrams that illustrate the development of a material for sale as an excipient, the approval of the use of an excipient in a dosage form, the negotiation process used to determine the appropriateness of the requirements, and the specific requirements for the excipient.

Each Phase of the process is also described by a flowchart illustrating the process:

Phase One- The Excipient supplier’s Process shows the steps a chemical manufacturer may take to evaluate the market and regulatory requirements for the proposed excipient and the steps leading up to the market launch,

Phase Two- The User’s Process illustrates the path a pharmaceutical company ordinarily follows in evaluating the excipient and its manufacturer for use in a formulation, and

Phase Three- The Negotiation Process shows the process by which the supplier and user interact to reach a mutual agreement on quality requirements.

As an international guidance document, the guide cannot specify all national legal requirements or cover in detail the particular characteristics of excipient qualification in all territories. Although the details in this document highlight European and United States issues, the principles can be applied to any excipient supplier – excipient user relationship worldwide.

By setting out all the stages in excipient qualification both suppliers and users will be better placed to use the tools in ICH Q9 Quality Risk Management[i] to better assess which steps in this guide are most appropriate and necessary for their particular situation.

[i] ICH Q9, *Quality Risk Management*, http://www.ich.org/LOB/media/MEDIA1957.pdf

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ACKNOWLEDGEMENTS

This Guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council (IPEC), an industry association whose members consist of **excipient** manufacturers, distributors, and pharmaceutical users. The company representatives who worked on this Guide are listed below:

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1. INTRODUCTION

1.1 Purpose

This document is meant as a guide for the qualification of excipient ingredients by excipient **suppliers** and pharmaceutical users. Its goal is to establish the information needed to support the introduction of a material for marketing as an excipient to the pharmaceutical industry as well as to indicate the steps used to establish the requirements for use of an excipient by a pharmaceutical company.

1.2 Scope

This guide is applicable to all excipients used in pharmaceutical dosage forms.

1.3 Principles Adopted

When considering how to use this guide, each excipient supplier must consider how it may apply to their material and processes. In addition pharmaceutical formulators should consider the proper use of the excipient in their formulation. Although the steps are laid out in a specific sequence in this guide, supplier and users are not required to follow that route through the excipient qualification process nor indeed cover every aspect described. The diversity of excipients means that some principles of the guide may not be applicable to certain materials and processes. The terminology "should" and "it is recommended" do not necessarily mean "must".

1.4 Layout

Flow diagrams are a pictorial display of the process described in detail in this document. They outline a logical path with sequential steps and appropriate decision points that should be evaluated in the excipient development and qualification process. Decision points show what the next phase of the evaluation would be, dependent upon the decision reached.

The reference number contained in the boxes of the flow diagram refers the reader to the corresponding section in this guide where further information is provided. The box number appears as bold text between the chevrons (**<number>**) in the text.

2. GENERAL GUIDANCE

2.1 Differentiation of Excipient Manufacture

Many materials used as excipients have applications other than in pharmaceuticals, such as food additives, cosmetics, or industrial products. Thus, environmental conditions, equipment, and operational techniques employed in excipient manufacture are often those of the chemical industry rather than those of the pharmaceutical industry. The excipient starting materials may not be required to be manufactured in accordance with **Good Manufacturing Practice** (GMP) requirements for excipients (for example as in the IPEC-PQG GMP Guide[1]) because these other uses of the material do not demand the adoption of GMP. Excipients may be manufactured through significant chemical change, physical modification, blending, or purification which causes many of the **other components** present in the starting materials to be removed or reduced. The effectiveness of these steps is confirmed by chemical, biological, or physical testing of the excipient. Once synthesized or isolated, excipients normally undergo additional purification. Thus while materials manufactured by the chemical industry, primarily for other applications can be used as pharmaceutical excipients, in these cases the principles of GMP will need to be applied when the material is intended for use in the pharmaceutical industry.

For distributors the same principles apply in that the purity, integrity, and suitability of the excipient for use in pharmaceutical products needs to be assured. In these cases the IPEC **Good Distribution Practice** (GDP) Guide[2] is an appropriate starting point for defining the quality assurance standards and systems required.

The finished dosage formulator is highly dependent on the excipient manufacturer to provide materials that are uniform in chemical and physical characteristics. This is particularly important in the context of the pharmaceutical product approval process where bioequivalence comparisons are made between pivotal, clinical trial batch ("biobatch") production and commercial scale-up lots. The excipient used to manufacture commercial lots should not differ significantly from those used in biobatches to provide adequate assurance of finished product performance. Therefore, it is important to minimize variation between the different batches of excipient, as well as within the excipient batch itself. However if significant differences do occur between excipient lots used in clinical and commercial drug product lots, additional testing by the finished dosage manufacturer may be required to establish the bioequivalence of the drug product.

The user of the excipient typically does not significantly alter the chemical and/or physical properties of the excipient prior to use. Consequently, other components present in the excipient are likely to be present in the drug product. Excipients frequently function because they are not "pure". That is to say that there may be **concomitant components** that are necessary for the correct functioning of the excipient. These concomitant components should not be confused with "**impurities**".[3]

Although dosage form manufacturers may have some limited control over excipient quality through specifications, the excipient manufacturer must be considered to have greater control over physical characteristics, quality, and the presence of other components in the excipient they produce. Control over other components in the excipient should not be taken to mean minimizing or even eliminating concomitant components from the excipient. The presence of concomitant components in the excipient often has a beneficial effect on excipient performance, but control is needed to assure that the presence of concomitant components is at a consistent level and other

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[1] *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006*
[2] *The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients*, 2006
[3] IPEC *Excipient Composition Guide* (in development)

components are kept to a minimum. It is important to remember however that it is the responsibility of the pharmaceutical dosage form manufacturer to ensure the safety of their drug product and the excipients used in the formulation.

Excipients are frequently used in different types of drug products where physical characteristics, such as particle size, may be important. While the pharmaceutical formulator is primarily responsible for identifying the particular physical characteristics needed, it is the responsibility of the excipient manufacturer to adequately control the excipient manufacturing process to assure consistent excipient conformance to the agreed specifications.

2.1.1 Reference Documents

Several sources have been used for reference information in the development of this guideline and are listed in Appendix C-Bibliography. IPEC has issued several guidelines that are referred to in this document. In addition, the pharmacopoeias have pertinent information in their general chapters that are applicable. Finally, several ICH[4] documents are referenced in various sections of this guideline (and are also included in Appendix C-Bibliography).

2.2 Preliminary Excipient Marketing Decision

The **original manufacturer** begins the process of offering a chemical to the pharmaceutical market as a substance suitable for use as an excipient in a drug product **<1.1>**. It is not appropriate for a distributor to make the determination to use a non-pharmaceutical grade as a drug component.

Alternatively, a pharmaceutical customer may approach the excipient supplier and indicate a desire to utilize their product as an excipient (see Section 4-Phase 2). In either instance the decision to provide the material as an excipient should be made with a good understanding of the suitability of the safety and quality of the material, and the ability to supply this quality on a consistent basis.

2.2.1 Determination of the Intended Target Market and Route of Administration

The intended end use of the excipient should be identified and considered in determining the appropriate regulatory and GMP requirements for the excipient and its manufacturing facility **<1.2>**. Of particular importance is whether the excipient will be a component of a finished drug product. The route of administration is critical to defining the requirements for the excipient because the key principle throughout pharmaceutical supply is that of protecting the patient. The risks to the patient are proportional to the route of administration, approximately increasing in the following sequence:

- Topical
- Oral, vaginal, and rectal
- Pulmonary/Inhalation
- Parenteral, ophthalmic, and preparations intended for use in open wounds

Parenteral dosage forms normally require an excipient to have a low bioburden or be produced as **pyrogen-free**. An excipient to be used in a **sterile** drug product may be required either to be sterile or capable of remaining unaffected by the drug manufacturer's sterilization process. The excipient supplier is responsible for ensuring that excipients meet bacterial **endotoxins** specifications or are pyrogen-free, only if the excipient manufacturer makes such a representation in specifications, labeling, contractual agreement, a **Drug**

[4] ICH *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*: http://www.ich.org

Master File (DMF), or a **Certificate of Suitability to the European Pharmacopeia** (CEP).

2.3 Regulatory Assessment

2.3.1 Safety, Toxicological, and Precedence of Use Issues

There are several safety related issues that should be assessed by the potential excipient manufacturer as part of their decision to introduce an excipient to the pharmaceutical market **<1.3>**.

First an assessment should be made as to whether there is a precedence of use for the material in a drug product or a similar application such as a food additive, food contact packaging component. If a precedence of use can be shown in applications where there is human exposure, the safety of the material might already be appropriate for potential application as an excipient in the pharmaceutical industry.

In the U.S., the Food and Drug Administration (FDA) maintains a database of excipients that is posted on their website as the Inactive Ingredient Database (IID) [5]. The IID should be used to establish precedence of use since it lists each excipient which has been allowed as a consequence of its presence in an approved innovator drug product. Each excipient is listed by name, dosage form, and the maximum amount of excipient contained in an approved drug of that listed dosage form. Care must be exercised in searching the database because an excipient can be listed by various names, including trade name, compendia name, chemical name, or generic description (for dyes and flavors).

In Japan, an assessment for precedence of use can be made by referring to the Japanese Pharmaceutical Excipients Dictionary (JPED) which is edited by the Japan Pharmaceutical Excipients Council in conjunction with the Ministry of Health, Labor, and Welfare. The JPED is a compilation of all excipients for which there is a precedence of use in drug products in Japan. It includes monographs from the JP or Japanese Pharmaceutical Excipients (JPE) as well as all non-monograph excipients that have been previously used. Each monograph lists the nonproprietary name and synonyms along with the application and maximum dosages for the various routes of administration in approved drugs[6].

In Europe, there is no comprehensive European Union list of excipients that have been approved in drug products. Therefore, in order to establish precedence of use, it is necessary to review the drug catalogues such as the "Dictionnaire Vidal" (France),"Die Rote Liste" (Germany), or "The Electronic Medicines Compendium" (UK)[7].

At the time this Guide was prepared, the European Union had mandated the application of GMP principles to "certain excipients"[8]. Materials in this category are those that could pose a higher safety risk to the patient including excipients:

- prepared from materials derived from a TSE-relevant animal species (excluding lactose)
- derived from human/animal material with potential viral contamination risk

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5 Instructions: http://www.fda.gov/cder/iig/iigfaqWEB.htm,
Database: http:www.accessdata.fda.gov/scripts/cder/iig/index.cgm

6 Maximum dosage information is only contained in the Japanese language version of the JPED.

7 Electronic Medicines Compendium; http://www.medicines.org.uk/emc.aspx

8 Draft: Specific Conditions of the Application of the Principles and Guidelines of Good Manufacturing Practice for Certain Excipients EC-Directive 2001/83/EC, as amended by EC-Directive 2004/27/EC

- claimed to be sterile (or sold as sterile) and used without further sterilization
- with the specification or claim that they are endotoxin/pyrogen controlled, or
- the following specific materials:
    - propylene glycol
    - glycerol

Following a public and industry consultation in the summer of 2007, an economic impact assessment suggested that it was not in the public benefit to mandate the application of GMP for certain excipients. However, a final decision has not been taken; nevertheless IPEC recommends the application of the GMP principles described in the IPEC-PQG Excipient GMP Guide to all excipients.

If there is no precedence of use in a drug product, then the material is to be considered a new excipient (see Sections 2.3.2 and 2.3.5).

2.3.2 New (Novel) Excipients

An excipient used for the first time in a drug product or by a new route of administration is classified as new according to the ICH Guideline M4[9], *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*. Conversely, this guideline defines known excipients as “excipients that are well-established and commonly used in registered drug products and are usually included in pharmacopoeias”.

When an excipient has not previously been used in a pharmaceutical dosage form then there are a number of conditions set out by the US and European regulatory authorities to allow for its use.

The U.S. FDA has issued a Guidance concerning the safety testing required for novel excipients[10] as has IPEC in their IPEC New Excipient Evaluation Guidelines dated October 1996[11] which were the basis for the USP-NF 26 General Chapter *Excipient Biological Safety Evaluation Guidelines* <1074>[12] on this topic. The information contained in these documents is useful for assessing the safety of a chemical for use as an excipient. The IPEC Europe Safety Committee has published a similar guideline[13]. The manufacturer of a new or novel excipient should develop the safety information recommended in these guidelines appropriate to their intended use. This information provides the basis for establishing the suitability of the material for use as an excipient in a particular type of dosage form.

The terms “new” and “novel” as related to excipients are difficult to define precisely. Clearly an excipient is new if it is not listed in:

- the FDA Inactive Ingredient database,
- any of the 3 major compendia, U.S. Pharmacopeia (*USP-NF*), European Pharmacopoeia (Ph. Eur.), or Japanese Pharmacopoeia (JP), or
- other widely known compendia such as the “Handbook of Pharmaceutical Excipients” or “Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete” (Encyclopedia of excipients for pharmaceutical, cosmetic

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9 ICH M4, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*, Step 4, 2004.

10 U.S. FDA, *Nonclinical Studies for Development of Pharmaceutical Excipients* (final version May 2005)

11 Steinberg, M., Borzelleca, J.F., Enters, E.K., Kinoshita, F.K., Loper, A., Mitchell, D.B., Tamulinas, C.B., and Weiner, M.L., *A New Approach to the Safety Assessment of Pharmaceutical Excipients,* Regulatory Toxicology and Pharmacology, 24, 2, 1996.

12 *USP-NF* General Chapter <1074> *Excipient Biological Safety Evaluation Guidelines*

13 *The Proposed Guidelines for the Safety Evaluation of New Excipients* (European Pharmaceutical Review, November 1997)

and related use).

The industry recognizes that any change in the chemical composition of an excipient produces a new excipient, no matter how minor the modification to the chemical composition. Mixtures of excipient ingredients can result in a novel excipient when the subject mixture is to be used in a dosage form for which its constituent excipients have not already independently been used in that intended route of administration. Physical modification of an excipient, such as micronizing or compaction does not generally produce a new or novel excipient.

However, co-processing can produce a synergistic physical interaction between two or more excipients that is patentable and create unique properties that cannot be achieved through simple blending[3]. The safety assessment for these co-processed excipients made with commonly used pharmaceutical excipients will generally be less stringent than for a new chemical entity.

If the excipient is already described in a pharmacopoeia or used as such in other pharmaceutical dosage forms, the excipient is neither new nor novel and the detailed safety review recommended in the above guidelines will not be necessary.

2.3.3 Compendial Requirements

General Comments

There are three major compendia that are routinely referenced globally; the United States Pharmacopeia – National Formulary (*USP-NF*), the European Pharmacopoeia (Ph.Eur.), and the Japanese Pharmacopoeia (JP). These compendia describe the quality of substances to be regularly used in pharmaceutical products, how to test them and the other general conditions required to assure the quality of pharmaceutical substances so that they are not harmful to the patient. The descriptions of substances for pharmaceutical use are called monographs and these list the analytical specification and other quality attributes required to assure the safety and quality of the excipient.

In order to market an excipient, there is no regulatory requirement that there must be a compendial monograph for the material. However, if a compendial monograph exists for an excipient in a particular region's pharmacopoeia, then the excipient should comply with that monograph because the regulatory authorities require conformance. However, other regulations may define a suitable quality which could be used (e.g. Food Chemical Codex). In all cases, the use of a specification that at least meets a compendial monograph or a similar standard is preferable to the supplier's own internal document. In particular conformance to a pharmacopoeial monograph and other relevant general notices and chapters of the compendia means that the excipient already has a suitably defined quality for pharmaceutical use.

In some instances, other specific regulations apply for a specific use such as for parenteral applications as discussed above (see Section 2.2.1).

In the United States, certain food additive materials are produced in conformance with the Food Chemical Codex (FCC) while in Japan, there is the Japanese Pharmaceutical Codex and also a series of supplementary books called the Japanese Pharmaceutical Excipients (JPE). Many other national pharmacopoeias delineate the quality requirements of pharmaceutical ingredients and these will take precedence over the three major pharmacopoeias.

Where an excipient is described in a pharmacopoeia, the quality of material for pharmaceutical use must comply with this monograph (regulatory requirement).

The compendia are concerned with the presence of **additives** and **processing aids** in excipients. While the issue is still under active consideration by the pharmacopoeias, it is suggested that excipient manufacturers compile information on the identity and quantity of additives and processing aids that are or may be present in excipient products.

For an excipient listed in multiple compendia that may be marketed for global use, the manufacturer is advised to ascertain the conformance of the excipient to the monograph requirements found in all those compendia. While considerable efforts are underway to harmonize the requirements for excipients with monographs in the three major compendia, currently there are often different monograph requirements found in one or more of these compendia. Even for excipients whose monographs have completed the harmonization process, they may still contain non-harmonized attributes. As a consequence, it is advisable to tabulate all monograph testing requirements from all compendia having an appropriate monograph. Such a table should contain not only the test name and specification range but a brief description of the test method since often the method of analysis differs between compendia. Once the tabulation is complete, the excipient supplier can develop a testing plan to ensure conformance to all monograph requirements in the various compendia. Where multiple test methods are referenced for the same property (attribute), it would be satisfactory to validate the manufacturer's method to demonstrate it provides assurance that the excipient, when tested to each monograph method, will conform to each monograph requirements.

The commercial relevance of an excipient and therefore the use of the excipient in at least one approved drug product is a prerequisite for inclusion of a monograph in the Ph.Eur., *USP-NF,* or JP/JPE. Both users and suppliers of excipients may request their local pharmacopeia to develop a new monograph once a material's use in a commercial pharmaceutical product has occurred. When there is no pharmacopoeia or other compendia monograph, the manufacturer can establish its own specification, based on an existing similar pharmacopoeia monograph. If not available, the specification can be based on its own experience and the excipient's chemical and physical properties and intended use.

United States Pharmacopeia– National Formulary

The USP and NF are legally separate compendia officially mandated in the U.S. Federal Food, Drug and Cosmetics Act. However, they are published together in a single book.

To be considered for inclusion in the *USP-NF*, a new excipient should have been used in an approved drug product or be listed in another pharmacopoeia. A monograph is prepared for the new excipient with input from both the excipient manufacturers and pharmaceutical users. The draft monograph is then published for comment in the Pharmacopeial Forum and then submitted to the USP for approval.

The *USP-NF* General Notices require the use of appropriate GMPs in the manufacture of compendial materials[14]. The *USP-NF* includes a General Information Chapter which elaborates on the GMP requirements for producing an excipient.[15] The *USP-NF* also specifies the requirements for properly testing an excipient both in terms of the

[14] *USP-NF* General Notices subsection Ingredients and Processes, second paragraph.
[15] *USP-NF* <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*

requirements for validated test methods as well as by detailing specific test methodology. Generally, excipient monographs (specifications) are contained in that portion of the *USP-NF* called the National Formulary (NF) unless they also have been used in a dosage form where they function as the **Active Pharmaceutical Ingredient** (API), in which case they are contained in the United States Pharmacopoeia (USP). The monographs detail the test methods and specification limits which must be achieved in order to market an excipient as compendial grade. Certain monographs also contain additional information such as labeling and storage requirements.

In order to label an excipient as compendial grade, regardless of the pharmacopoeia, all monograph and appropriate General Chapter or Notices requirements ordinarily must be met. There is an exception to this for USP and NF grade excipients, under certain circumstances, as noted in the *USP-NF* General Notices[16]. Nevertheless, alternative test methods used must be validated[17] and shown to produce results comparable to those obtained using the compendial method. Non-compendial test methods used must be validated.

European Pharmacopoeia

For a new excipient to be added to Ph.Eur. it must have been a component of a previously approved drug product and no longer protected by patent. The drug product formulated with the new excipient ingredient is reviewed and approved by the member state or states to which the application has been submitted. Once used in an approved drug product, to be added to the Ph.Eur. the new excipient; must be included in the work program of the European Pharmacopoeia Commission. To be added to the work program typically requires the support of several member states at the biannual meeting of the Commission. The excipient is usually assigned to an expert group and the secretariat will identify the excipient manufacturers. The excipient suppliers are then asked to provide specifications, test methods, and samples from which the expert group will develop a draft monograph for public review by publication in PharmEuropa and subsequent approval by the European Pharmacopoeia Commission. Upon approval by the Commission, the excipient is added to Ph.Eur.

Japanese Pharmacopoeia

In Japan, new excipients are also approved as a consequence of the approval of a drug product application containing the excipient. The pharmaceutical manufacturer makes an application through a prefectural office to the Pharmaceuticals and Medical Devices Agency (PMDA). If the drug formulation contains an excipient with no precedence of use in Japan, the application goes to the Subcommittee on Pharmaceutical Excipients of the Central Pharmaceutical Affairs Council (CPAC). Their review of the quality attributes and safety of the excipient is done concurrently with the drug product approval conducted by the Subcommittee on New Drugs of CPAC. The Subcommittee reports are used by the Evaluation and Licensing Division to approve the drug product. Once the drug product has been approved, the Japanese Pharmacopoeia can consider the addition of a monograph.

New and Novel Excipients not listed in a Pharmacopoeia

An ingredient can be used in a pharmaceutical product as an excipient even when there is no monograph for the material in a compendium. Regulatory authorities require a full safety and toxicological evaluation[10, 11,12,13]. Once a regulatory authority has approved a drug application containing such an excipient, that excipient is generally considered

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[16] *USP-NF* General Notices subsection Official and Official Articles, fourth paragraph.
[17] *USP-NF* <1225> *Validation of Compendial Methods*

acceptable for the same route of administration up to the same level of use providing the same specifications are met as those used in the previously approved drug.

For new excipients a toxicological assessment should be made to demonstrate the safety of the material in the intended pharmaceutical application at the specified use level. The *USP-NF* Excipient Biological Safety Evaluation Guidelines <1074>[12] provides guidance on conducting a safety assessment for a novel excipient. In the U.S., the FDA has also issued guidance on non-clinical studies for new excipients[10].

When new excipients are developed and being used in an approved drug, the manufacturer may request that a monograph for the excipient is added to the compendia. "The purpose of a pharmacopoeial excipient monograph is to provide standards to assure the excipient's quality in pharmaceutical use." "The tests, procedures, and acceptance criteria for an excipient specification should address: appearance, identity, chemical purity, microbiological purity, physical characteristics (e.g., optical rotation), packaging, labeling, and storage."[18]

Generally an excipient monograph contains the following information[19]:

- Monograph Name: The name by which the excipient will be primarily found in the compendia,
- Official Title: The name by which the excipient is generally known in industry,
- Definition: The acceptance criteria for the assay often expressed as a percentage range,
- Packaging and Storage: Special packaging or storage conditions necessary to protect the excipient,
- Labeling: Special requirements for labeling to differentiate various grades of the excipient such as by molecular weight or listing of additives present,
- Description: The excipient is characterized as to chemical structure, molecular weight, physical form, and solubility,
- Identification: There should be a test or tests that confirm the identity of the excipient,
- Composition: There should be specific tests, where possible, for concomitant and other components especially for those above 0.1%. There should be tests, where appropriate, for organic, inorganic and heavy metal components as well as residual solvent(s),
- Assay: There should be a test to quantify the excipient content, where possible, and
- Other tests: Where further characterization is needed, other tests such as pH, preservative content, or bacterial endotoxin should be recommended.

The European Medicines Agency (EMEA) also requires for excipients not in the Ph.Eur.[20]:

- Physical Characteristics
- Tests for parameters that may influence the performance in the dosage form called functionality-related characteristics.

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[18] Guideline for Submitting Requests for Revision of the *USP-NF*, Chapter Three Excipients, page 67 October 8, 2003

[19] Guideline for Submitting Requests for Revision of the *USP-NF*, Chapter Three Excipients, pp 57-64 October 8, 2003

[20] The European Agency for the Evaluation of Medicinal Products, *Evaluation of Medicines for Human Use*, Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, (DRAFT) CPMP/QWP/419/03, February 2003

This list is not exhaustive but is intended to provide preliminary guidance on the content of a proposed monograph.

In addition, the manufacturer will have to submit information about the appearance and solubility characteristics of the new excipient. This information appears in a separate section of the *USP-NF*. In Europe, the user will also have to justify the specifications for the excipient. For new or novel excipients, there should be documentation in accordance with their "Guideline on The Chemistry of New Active Substances"[21].

Other regulatory requirements

Although the monographs specify the characteristics an excipient must meet in order to be used in pharmaceutical applications, there are other requirements which can be found in the General Notices and/or General Chapters and which can apply if the criteria are met. Some of these are described in Section 2.3.6.

2.3.4 Desired Properties for Intended Use

The initial step in bringing a new excipient to market is to determine its **functionality** as required in the manufacture, administration, identification, or stability of the intended drug product.

Suppliers may have a range of data available describing the functionality of their materials if they have been used in other applications, e.g., food, cosmetics. This information can be valuable to pharmaceutical users as it will help define the functionality and to some degree the safety profile of the excipient. Some of this data and knowledge can be considered proprietary. If it is to be shared with excipient users, suitable confidentiality agreements may need to be drawn up.

For genuinely new materials that are to be used as excipients, the corresponding data would need to be generated to show the utility of the material in the intended applications.

2.3.5 Excipient Master Files and Other Filings

A Drug Master File (DMF) is a compilation of technical details related to the manufacture of the excipient and is formatted so that it is aligned with the ICH Common Technical Document (CTD) format for easy future application. The DMF typically includes specifications and test methods for raw materials, in-process testing, and the finished excipient product, a complete description of the manufacturing process, safety data, packaging details, and label content.

In the U.S., an excipient supplier will often submit a DMF to the Food and Drug Administration to provide confidential information relative to the excipient, its safety, and conformance with appropriate GMP requirements. A similar system of DMF exists in both Canada and Japan. In Europe, for materials where a Certificate of Suitability is not available, such confidential information needed to support the drug product filing by a pharmaceutical manufacturer must be supplied directly to the user for inclusion in their marketing authorization, using confidentiality agreements where necessary.

United States Drug Master Files

Submission of an excipient Drug Master File (DMF) to the FDA is not required by law or FDA regulations[22]. A Type IV DMF for Chemistry, Manufacturing and Controls (CMC)

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[21] The European Agency for the Evaluation of Medicinal Products, *Guideline on The Chemistry of New Active Substances*, CPMP/QWP/130/96/Rev 1, February 2004

[22] FDA *Guideline for Drug Master Files*, September 1989.

information, or a Type V DMF for excipient safety information can be used to submit this type of data. The DMF may be used to support an Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biological License Application (BLA), Veterinary Drug Application, another DMF, or an Export Application. The FDA assigns a unique number to the DMF but does not approve or disapprove them. The FDA maintains the DMF as a confidential document that cannot be referenced by third parties without the written agreement of the excipient DMF holder.

The FDA references the DMF only in conjunction with their review of a submission or application to the FDA in the form of a drug application (IND, NDA, ANDA etc.). The review occurs when the excipient DMF holder has given the drug formulator permission to reference the DMF in their drug filing to the FDA. In the FDA review of the drug filing, when the agency requires details concerning the manufacture of the excipient, the FDA will review the information in the DMF. The excipient DMF holder has the obligation to assure the content of their DMF remains current and should update the DMF on an annual basis or indicate to the FDA that no changes are required.

IPEC has issued a guideline that describes the organization and composition of an excipient DMF[23].

These types of systems are also being considered in other regions at this time and could be implemented elsewhere in the future.

European Certificates of Suitability (CEP)

The system in the European Union (EU) is somewhat different from other areas. There are three types of marketing authorization procedures for drug products which use DMFs or CEPs as applicable:

1. Centralized (submission to the European Medicines Agency EMEA, London, UK obligatory for biological and biotech products, certain therapeutic indications and open to innovations), two countries identified as rapporteur and co-rapporteur each evaluating the dossier.
2. Mutual Recognition Procedure (MRP - submission to and approval by one EU member state which then becomes the reference country for extension within the EU).
3. Decentralized procedure (submission to all EU countries desired, one of them identified as the reference country. The procedure is similar to, but quicker than, the MRP).

No matter which procedure applies, pertinent excipient data must be provided directly to the pharmaceutical company for inclusion in their drug product dossier. It is recommended that it be provided under a suitable confidentiality agreement.

Although a DMF system exists for drug substances (APIs) at this time this system is not available for excipients.

There are two types of CEP; the “ordinary” one can be obtained by excipient manufacturers for an excipient described in a Ph.Eur. monograph by submitting a file using the Common Technical Document (CTD) format to the European Directorate for the Quality of Medicines (EDQM) in Strasbourg, France. The CEP acts in much the same way as a U.S. Type IV Drug Master file and allows the excipient supplier to retain confidential

[23] IPEC-Americas, *Excipient Master File Guide*, 2004.

information which is not shared with the excipient user. These Certificates of Suitability are not available for excipients for which there is no monograph in the Ph.Eur.

A second type of CEP exists to document that there is no potential concern about Transmissible Spongiform Encephalopathies (TSE; including Bovine Spongiform Encephalopathy - BSE) which is open to APIs and excipients (even those without a pharmacopoeia monograph). Granting the CEP indicates that the excipient is of low or no risk of transmission of TSE to humans through the drug product.

Japanese Drug Master Files

In Japan the drug product application is submitted to the regulatory authorities by the pharmaceutical company typically containing all relevant details concerning the excipient. The new excipient Drug Master File system in Japan can be used in certain circumstances; however this system is still undergoing some changes to allow it to be used for all types of excipients and applications. Currently, this system can be used fairly easily for individual excipients. However, it is not designed to easily handle multiple excipient grades or combinations of excipients which are part of a range of products that comprise an excipient family. Since a unique file would be needed for each formulation or grade, this makes the system somewhat burdensome.

2.3.6 International Conference on Harmonisation (ICH)

The International Conference on Harmonisation (ICH) was organized to develop uniform global requirements for various technical aspects of pharmaceutical product registration. ICH has approved guidance documents on the technical requirements for drug products containing new ingredients. While the focus is primarily on the dosage form and active ingredients, several of the guidelines have an impact on excipients and can affect the marketing of an excipient. Excipient suppliers should familiarize themselves with the following two documents as pharmaceutical customers will expect to see compliance to these guidelines.

2.3.6.1 Q3A, *Impurities in New Drug Substances*

ICH has issued the Q3A guideline[24] for drug substances which recommends steps for qualifying impurities in the active pharmaceutical ingredient. Since such materials when found in excipients are often beneficial to excipient performance, they are referred to as other components. While ICH Q3A guideline is not specifically intended for excipients, it is suggested that other components which are potentially harmful or do not contribute to the performance of the excipient are identified and reported using the provisions of the guideline. Where appropriate, consideration should be given to establishing specification limits for certain other components. It is suggested that a **composition profile**[3] is developed so that:

- The potential for drug interactions with other components can be determined by the user.
- The impact on the composition can be assessed following changes to:
  - The Manufacturing Process
  - Raw materials
  - Packaging

The composition profile defines all components that comprise the excipient.

2.3.6.2 Q3C, *Impurities: Guideline for Residual Solvents*

[24] ICH Q3A, *Impurities in New Drug Substances*, http://www.ich.org/LOB/media/MEDIA422.pdf

ICH has also issued the Q3C guideline[25] on residual solvents which lists various organic solvents in one of four classifications. They include solvents to be avoided, solvents to be limited, solvents with low toxic potential, and solvents for which no adequate toxicological data was found. The presence in the excipient of any solvent listed in the ICH guideline should be within the limits specified in the guideline for the intended application. However, it is important to note that these levels are for the presence of the stated solvent in the finished dosage form and not in the individual excipient ingredients. Therefore, in calculating the maximum allowable residual solvent level in the excipient, the intended use concentration of the excipient in the finished dosage form along with other sources of the listed solvent must be taken into account. Residual solvents should be limited as much as possible in the excipients so that they are below those listed in Q3C or are present only very low levels in the drug product. This will then reduce or limit the need for routine testing of residual solvents in the drug product, except for those used in its manufacture. If the level of residual solvent exceeds those in the Q3C guideline, the manufacturer should measure and report the quantity of the residual solvent in each lot of excipient and report on the COA. In the absence of information concerning the usage level of the excipient in the drug product, the levels in Q3C should be adopted.

This ICH guideline for Residual Solvents has been adopted by the Ph.Eur. as Chapter 5.4, and the USP has replaced the General Chapter Organic Volatile Impurities <467> with the Q3C text which is now General Chapter Residual Solvents <467>.

2.3.7 Specific Safety Issues

Depending on applicability, excipient suppliers should have knowledge of and control over the following aspects of excipient quality since they may also have implications for end user safety:

- Origin of raw materials
  - Animal derived materials lead to concern for issues related to BSE or other TSE which can restrict acceptance. Issues may also arise if raw materials are derived from certain other natural substances (e.g. peanuts) since some of these materials can lead to allergic reactions in the patient. Finally, concerns may arise about excipients produced from genetically modified organisms (GMOs) such as corn (maize) or soy products. These issues may restrict the acceptance and use of excipients. It is therefore critical that the excipient supplier determines and controls the origin of their raw materials.
  - Viral safety information may be needed in case of excipient raw materials of human or animal origin. For such materials, viral safety evaluation study results may be required. They should demonstrate that materials used in production of the excipient are considered safe and that the approaches (methods) used to test, evaluate, and eliminate potential risks during the manufacturing are suitable.
- Degradation products of the excipient
  - For a well established excipient, the excipient supplier will often know how it changes as a result of atypical processing conditions or due to thermal and related stresses to which it may be exposed in the supply chain. Such

[25] ICH Q3C, *Impurities, Guideline for Residual Solvents*, http://www.ich.org/LOB/media/MEDIA423.pdf

knowledge should be made available to the user. Where formal stability studies on the excipient are conducted, such studies can provide similar information (see Section 2.5.1).

- Presence of catalyst residue, decomposition or degradation products, and process related components. This is particularly relevant where the catalyst residues are heavy metals[26].
- Inclusion of additives and processing aids
    - The presence of additives and process aids in the excipient such as biocides, anti-oxidants, or stabilizers can lead to safety concerns for the user, and their selection should be carefully reviewed and assessed for acceptability in the intended market application. A composition profile should be developed for the purpose of establishing the presence of process- related components and the quantity present. The excipient supplier should endeavor to provide a consistent quantity of these components in the excipient.

While safety issues such as these may be evident in the excipient, it is not suggested that this precludes their acceptance in all instances. It is important that the original manufacturer evaluates their effect as part of the regulatory assessment.

2.3.8 Concluding Comments on the Regulatory Assessment

Upon the completion of regulatory assessment, the market minimum requirements should have been established along with any "regulatory" constraints **<1.4>**. To proceed with the introduction of the excipient, the conclusion of the evaluation should be that the material can be suitably produced for the intended use. If not, the project should be discontinued **<1.5>**.

2.4 Manufacturing and Packaging

From the point where GMP starts[27], all operations including packaging and distribution should be conducted in conformance with appropriate excipient GMP or GDP requirements **<1.6>**.

It is important that the excipient is produced using a manufacturing process that is in a state of control, often referred to as a capable process. Whether the process is by batch or continuous, there should be a written set of manufacturing instructions listing the raw materials, operating equipment, operating conditions, in-process controls, sampling plan, packaging operations, packaging components, and labeling materials with their content. While dedicated manufacturing equipment is preferred, multi-use equipment is acceptable provided there is no incidental carryover of **contaminants** from the manufacture of another chemical **<1.6>**.

Packaging operations include steps in the manufacturing process where the excipient may be exposed to potential environmental contamination, which raises another potential GMP compliance issue. Suitable controls need to be put in place in this area to ensure excipient quality. It is recommended that a quality risk assessment is conducted to ascertain the optimum controls in question **<1.7>.**

Packaging and labeling materials should also be considered. Packaging materials should be shown to suitably protect the excipient from potential environmental contamination and degradation while minimizing potential excipient contamination due to packaging components.

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[26] See EMEA Note for Guidance *Guideline on the Specifications Limits for Residues of Metal Catalysts or Metal Reagents*, EMEA/CHMP/SWP/4446/2000

[27] The Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients*, 2006, p 3

The container label should list the following as a minimum:

- The manufacturer's trade name
- The grade, if applicable
- The manufacturer's and/or distributor's name
- The batch number
- Special storage conditions required to assure excipient quality

As required, excipient labeling, which is inclusive of the container label, **Certificate of Analysis** (COA)[28], and **Bill of Lading** (BOL)[29], should also contain the following:

- The identification of all added substances such as preservatives or antimicrobials,
- Suggested storage conditions other than typical warehousing (ambient conditions),
- Special customer-requested information such as the customer raw material code, Kosher or Halal compliance, and
- Clear identification of the manufacturing plant site.

This information can be applied either at the site of manufacture or prior to final shipment to the pharmaceutical customer. For bulk shipments, the label content can appear on a combination of the Bill of Lading and the vehicle placard (where regulations on showing safety information permit such additions).

The manufacturing process, including packaging and labeling operations should be evaluated for their conformance to appropriate GMP requirements **<1.8>**. The excipient container should be sealed with a tamper-evident device. Such devices include security tape, embossed metal seals (for bulk shipments), and embossed bung seals.

2.4.1 Process Capability and Validation

The process for manufacturing the excipient should be capable of producing an excipient that consistently meets the established specifications. In the chemical processing industry, this is often referred to as having a capable process **<1.9>**. Demonstration that a process is capable is called a validation study in the pharmaceutical industry and often referred to as a **process capability** study in the chemical/excipient industry.

Capability is often determined by producing several batches using the manufacturing instructions. A **Process Validation** study, a requirement in the pharmaceutical industry, begins with the preparation and approval of a Process Validation protocol. The protocol delineates the details of the process validation study including a description of the equipment, process, sampling plan, and the validation approval criteria. The protocol is reviewed and approved and then the study is executed. A final report is prepared to document the study and its conclusions. The report is reviewed and approved by appropriate quality personnel.

As an alternative to a process validation study, statistical techniques can be used to demonstrate that the process capability is sufficient so that lot selection of excipient grade material is unnecessary. A useful and effective means of performing this is to determine the Process Capability Index (C_p and C_{pk}). C_p is a statistical measure of the ability of the process to generate batches near the midpoint of the specification, with numbers greater than 1.3 being typically deemed "capable", i.e. a process whose output meets specification with a likelihood of 99.7%. C_{pk} is a measure of how far the average value of the process is from the center of the specification. If it is identical to C_p, then the process is perfectly centered. Lower values indicate a process that is skewed to one side or the other of the

[28] IPEC-Americas *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*, 2000.

[29] A document used when shipping goods that describes the content of the shipment and accompanies it.

specification midpoint. These studies rely upon the process to be performing with only random variation. The process capability study should be documented and should satisfy the requirements to demonstrate that the manufacturing process is in control. This provides assurance to users that the quality of each batch of excipient will be consistent (see also Section 5.4).

If the process fails to reliably produce acceptable excipient, i.e. the process capability is too low, or the process validation failed, the manufacturer should consider modifications to process parameters and assess controls **<1.10>**. Since a lower process capability can result from problems with the test method, an assessment of the analytical methods may also be needed **<1.11**>. It is undesirable to select individual lots of material meeting excipient requirements (see Section 5.4.1). Therefore if the methods are satisfactory and the process cannot be adjusted to achieve the required process capability **<1.12>,** the manufacturer should reevaluate the suitability of using the chemical as an excipient for the target market, including the route of administration of the dosage form**<1.2>**. It is not normally acceptable to increase the specification limits in order to obtain a capable process.

2.4.2 Test Methods and Validation

In conjunction with the development of a suitable manufacturing process, the excipient producer should develop appropriate Quality Control test methods. Where the excipient is labeled as conforming to a compendial monograph, these test methods must either utilize the method described in the monograph or be demonstrated to provide comparable results. Test methods that do not follow all of the details described in the monograph should be validated. This requires documented scientific evidence showing the manufacturer's method adequately assures the excipient meets the designated monograph specification parameter.

For excipients listed in a regional compendium, the material is expected to conform to that monograph when used in that region. If other methods are developed and deemed more satisfactory, they must be validated against the compendia method and found to be equivalent to or better than the compendia method. Their use should be justified**.** It is important to note that where there is a discrepancy between the results obtained using the compendia method and the manufacturer's method, the compendia method is considered the official result.

Often an excipient manufacturer will develop its own test method for various reasons such as to provide assurance the excipient meets the intended performance requirements or to monitor or control the presence of other components. These non-compendial methods should meet the requirements for an appropriate test method as detailed in the compendia.

Test methods fall into two categories; those which can and those which cannot be validated. Examples of methods which cannot be validated include measurements, usually involving physical methods, such as bulk density, viscosity, and refractive index which rely on direct measurement using calibrated devices. Such methods cannot be validated in the classical sense.

The other category is for methods which can be validated. There should be a validation protocol and report for all methods that are non-compendial. The validation protocol should describe the study in order to show the method is appropriate including such details as a description of the test method, the equipment, reagents, standards etc. The protocol should also delineate the test results that must be achieved in order to consider the method validated. Once the validation has been conducted, there should be a report documenting the test results and conclusion. Test method validation may include evaluation of items

such as accuracy, precision, specificity, method linearity, ruggedness, limit of detection and limit of quantitation. ICH Q2 validation guidance[30] provides additional details on validation.

2.5 Excipient Specifications

A specification is a list of tests to be carried out and criteria to be met, in line with the established substance (or product) monograph (see also subsection 2.3.2 “New (Novel) Excipients”).

Draft or tentative specifications should be developed that are in accordance with accepted standards and are consistent with the manufacturing process and its process capability **<1.13>**. The excipients’ end use should also be considered, e.g., oral, sterile, dermal, in establishing these specifications. The specifications should include control of the composition (e.g. organic components, inorganic components, and residual solvents) related to both the raw materials and the manufacturing process. As necessary, appropriate limits for total microbial counts and compendial indicator organisms should be established based on the likelihood for microbial contamination and the ability of the excipient to support microbial growth. If the excipient is intended for use in parenteral drug products, appropriate limits should also be established for endotoxins.

Where the excipient is to be a compendial grade, the specification test methods should either follow the compendial methods as written, or be validated (if appropriate as noted in Section 2.4.2) to demonstrate scientifically that they produce comparable results. If the excipient is not compendial, then the test method should conform to the general requirements described in compendia or ICH guidelines on validation of analytical methods. The suitability of all test methods should nonetheless be verified under actual conditions of use and documented. The detection limit for each method should be sufficiently sensitive to discriminate between acceptable and unacceptable material, if appropriate.

The draft specification for compendial excipients should contain specified ranges for all parameters that assure the excipient meets the compendial requirements. If the excipient is not compendial, then the specified ranges should assure the excipient meets the technical and regulatory requirements appropriate to the use and route of administration.

Consideration should be given to the development of specifications that reflect customer requirements and those needed to assure adequate control of the excipient for its intended use. The specification should include those properties and specified ranges, within the process capability, necessary for the excipient to meet the customer’s use requirements.

2.5.1 Excipient Stability

It is important to demonstrate that the excipient remains in conformance with the sales specification until the end of the **re-evaluation interval**, **retest interval** or **expiration period**. The excipient supplier should provide data to show stability in the commercial packaging and defined storage conditions that are intended to protect the excipient from degradation throughout the supply chain[31]. If stability data is not available, the excipient user may have to generate it themselves **<1.14>**.

Preliminary information can be developed using accelerated stability protocols and conditions described in the ICH guideline Q1A *Stability Testing of New Drug Substances*

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[30] ICH Q2, *Validation of Analytical Procedures: Text and Methodology*, http://www.ich.org/LOB/media/MEDIA417.pdf

[31] IPEC Stability Guide (in development)

and Products[32]. Although this guideline was developed for drug substances (APIs) and drug products it is suggested that the stability of new excipients be evaluated according to the concepts of the guideline. It is important to determine the length of time the excipient will continue to meet the established specification in the unopened market package, referred to as the re-evaluation interval, retest interval or expiration period.

Ideally, the excipient re-evaluation interval or expiration period should be sufficiently long to allow the excipient user to receive and use the excipient prior to expiry **<1.15>**. Many pharmaceutical manufacturers desire excipients with a minimum re-evaluation interval exceeding one year. However, excipients may be considered suitable with shorter intervals provided appropriate controls are in place to ensure the excipient is used while in conformance with the specification. If this is not the case, then special arrangements may have to be made, for example temperature controlled storage and transportation, manufacture to order. Alternatively, it may be necessary, where appropriate (and if not a compendia, safety, or regulatory requirement), to adjust or broaden the specification range(s) so as to extend the re-evaluation interval or expiration period if possible **<1.16>**.

If the excipient is not sufficiently stable for the intended application, a study should be conducted to assess the possibility of improving the excipient stability **<1.17>** through process adjustment **<1.12>**. However, it is necessary to ensure the excipient continues to meet the expected technical and regulatory requirements. If the excipient stability cannot be sufficiently improved, it is unlikely the excipients would be accepted in the market place, and the manufacturer would be advised to re-consider their strategy **<1.2>**.

Ideally, samples of three commercial lots of the excipient should be used to establish the stability of the excipient in the commercial package. Samples of the excipient from these lots should be stored in commercial or **worst case** packaging material under the recommended storage conditions[31] (see the Stability Guide for more details). Periodically, excipient should be sampled from the three lots and tested for conformance to the sales specification and/or stability indicating tests to demonstrate continued conformance through the stated expiration period.

As an alternative to conducting a stability study under recommended storage conditions, which will take the full stated expiration period to complete, an accelerated stability study can be conducted. ICH has issued a guideline Q1A[32], which, while focusing on the API and dosage forms, provides guidance on test conditions also useful for excipients.

In either approach, stability indicating test(s) are desirable to monitor the impact of storage conditions on the excipient. A stability indicating test method is one where the measurement is capable of quantifying the degradation of the excipient. In the absence of a stability indicating method, testing to those parameters that are indicative of excipient stability and expected degradation (e.g. color) can be used.

3. EXCIPIENT DEVELOPMENT AND SPECIFICATION PROCESS

3.1 Excipient Consistency and Control

Each step of the excipient manufacturing process should be controlled, to the extent necessary, to ensure that the excipient consistently meets required specifications **<1.18>**. Various experimental strategies are available for identification of these operating parameters. One technique to identify

[32] ICH Q1A, *Stability Testing of New Drug Substances and Products* http://www.ich.org/LOB/media/MEDIA419.pdf

these parameters is use of a **Design of Experiments** (DoE) protocol[33]. Such experimentation can provide the basis for performing a process capability study to support process validation.

Excipients are normally subject to various in-process tests **<1.24>** (See Flow Diagram, Phase One, Page 2) to show that a manufacturing process is in a state of control. Based upon the operating parameters, a plan for process control should be developed. In-process inspection and testing should be performed based upon monitoring the process or actual sample analysis at defined controlled points and times. The plan should identify what in-process measurements should be made to monitor the process, what measurement techniques will be utilized, where and how any necessary process samples will be taken, and who will perform the testing (see also sections 2.4.1 and 5.4).

It is important to identify and set appropriate limits for excipient components. Such components arise from their presence in raw materials or their development during the manufacturing process either as by-products or residues from a catalyst, solvent, polymer initiator etc. These limits should be based upon appropriate toxicological data, or limits described in compendia, as well as considering the manufacturing processes and reaction chemistries.

The excipient supplier should have sufficient information at this point to evaluate the target market and use, and confirm that the business potential is sufficient to proceed with excipient development **<1.19>**. In addition, the manufacturer should confirm that the process is suitable to consistently produce a material that meets the market needs. If the information fails to confirm the market potential, the supplier may decide to discontinue the project **<1.20>**.

3.2 Performance Indicators

An excipient is included in a drug product because it performs a role in the formulation. Conformance to monograph requirements or product specifications is sufficient to establish consistency in the quality of the excipient **<1.21>**. However such testing may not establish that a change in the manufacturing process has altered its performance in the dosage form. Therefore for the purpose of evaluating process changes, appropriate performance indicators should be established, for the intended target use.

As an example, if the intended target use is solid dosage forms, several tests have been developed for use in establishing the performance characteristics of the dosage form, such as dissolution testing and tablet hardness. In this example, the excipient manufacturer might determine a baseline of these performance characteristics for the excipient in the target dosage form, e.g. using a model formulation. The excipients' performance characteristics might then be correlated with its physical properties such as particle size, particle shape, particle size distribution, specific gravity, viscosity, the hygroscopic nature of the excipient, etc. It is also possible that these characteristics might be correlated with the chemical composition such as the level of concomitant and other components. The excipient manufacturer would be able to evaluate the impact of a process change by comparing these excipient properties before and after the change to ensure consistent excipient performance.

Assessing excipient performance is an inexact science. Therefore, for most critical end-use applications, a strong collaboration with the excipient user is recommended so that this issue can be addressed.

3.3 Production Specification and Master Batch Record

Specifications for the manufacture and for the sale of the excipient should be developed. As noted earlier, the sales specification should meet the regulatory and market requirements for the

[33] IPEC QbD Guide (in development)

excipient **<1.22>**. The **production specification** delineates the requirements that the excipient must meet to assure not only conformance with the sales specification developed in Section 2.5 but also to assure conformance to regulatory requirements **<1.23>**. For example, a production specification may require demonstration that certain other components fall below established limits which the manufacturer may not wish to disclose to the customer in the sales specification. Specification limits for certain parameters appearing on both sets of specifications may be tighter on the production specification to ensure that the excipient continues to meet the sales specification limit throughout the re-evaluation interval.

For materials manufactured using batch processing, the **Master Batch Record** should be developed at this stage. Clear and complete manufacturing instructions help ensure uniform product quality. It should identify the raw materials, describe the process for manufacturing the excipient, identify GMP instruments and manufacturing equipment and their operating parameters, the in-process sampling and test requirements **<1.24>**, and describe the packaging and labeling of the excipient.

The **Master Production Record** documents all of the information needed to produce an excipient lot/batch. The record confirms the step-by-step progress in manufacturing the lot of excipient to the Master Batch Record. It should contain records of such items as the lot number and quantity of all raw materials used, the start and stop time for process steps requiring a specified duration, measurements made during the process, sampling intervals and test results where indicated (in-process controls), and the quantity of the excipient produced. For each entry on the production record there should be an indication of the person recording the information.

Where the excipient is produced using continuous processing, the Master Production Record should contain appropriate relevant information. The aim is to ensure that the critical processing aspects are recorded to demonstrate that the batch/lot has been manufactured according to the planned arrangements. Often this information is contained in log sheets or electronic files which record the process parameters and measurements on a periodic basis. Such information may be presented in a **Master Process Flow**, or a **Master Process Log**.

3.4 Marketing Materials

A literature package should be prepared for distribution to potential customers. The package should contain the sales specification (or draft as appropriate), Material Safety Data Sheet (MSDS), an Excipient Information Package (EIP)[34] **<1.25>**, and technical (promotional) literature including storage and stability information (as available) **<1.26>**.

Technical literature should be prepared describing the performance of the excipient for the target market, intended use, and the intended route of administration. The literature should clearly identify the material as an excipient and demonstrate the advantage(s) in using the excipient or the benefit derived from developing a drug formulation using the excipient. All labeling, technical, and promotional literature should be periodically reviewed to ensure that they are aligned with the excipient manufacturer's intended use of the excipient.

Certain excipients may also have been used by drug manufacturers as an API. Such applications tend to be historic and in some cases the excipient supplier is either unaware of the dual classification of their product or does not support the materials use as an API. At this time the legal position is clear, an API should be manufactured according to the GMP defined in ICH Q7[35]. In the U.S., the manufacturing site is required to be registered with the FDA as a 'drug

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[34] IPEC-Americas *Standardized Excipient Information Protocol User Guide*, 2005

[35] ICH Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* http://www.ich.org/LOB/media/MEDIA433.pdf

manufacturing establishment' as stated in Section 201 of the Federal Food, Drug and Cosmetic Act (FD&C Act). In Europe likewise, API manufacturers have to work according to ICH Q7 (elaborated as Part II in European GMPs), and for APIs imported from non-EU countries, GMP manufacturing must be audited and confirmed. Clearly, this meets or exceeds all requirements for an excipient. Where it is known that a material has the dual application, the excipient supplier should clearly indicate the intended application in marketing materials and on labeling.

The excipient supplier should begin to establish a formal system to answer customer inquiries concerning the excipient. In addition to the information contained in the EIP, the customer may require additional information on the excipient such as:

- Safety
  - Toxicology studies
  - Precedence of use
  - Human exposure data
  - Literature reviews, etc.
  - Animal testing
- Regulatory Status
  - Details of the regulatory status in specific target countries.
    - Note: It is the pharmaceutical formulator's or the pharmaceutical user company's responsibility to ensure the excipient meets regulatory requirements.

3.4.1 Sampling Guidelines

Sampling of excipient ingredients by the user is often critical to their obtaining proper Quality Control test results. Therefore, the excipient supplier may prepare sampling guidelines. Such guidelines should begin with an indication as to the homogeneity of the excipient in the package, as received by the customer. A sampling technique could be developed based on the homogeneity characteristics of the excipient, so as to assure a representative sample from the packaged excipient is taken. Where the quality of the excipient is affected by the sampling technique, such as moisture absorption for a hygroscopic excipient, additional guidance should be provided.

Traditionally, users have required samples of excipient from at least three discreet production lots for their evaluation **<1.27>**. While a customer may evaluate the performance characteristics of the excipient produced in the lab or a pilot plant, full evaluation by the pharmaceutical formulator will generally require excipient produced under appropriate GMP requirements in a commercial scale facility. For excipients produced in batch processes, it has been common to have these three commercial lots representing the extremes of the process, so as to demonstrate to the customer satisfactory performance within the range represented by the excipient sales specification (e.g. at the limits of one or more critical parameters that define excipient quality). Where such samples are unavailable, other techniques for assessing the excipient should be used (see Section 4).

The reliance on three lots of a new excipient for validation purposes is now changing. The Regulatory Agencies, particularly in the US with the introduction of **Quality by Design**[36] (QbD) and the **Design Space** concept, recognize that three lots may not be the appropriate number. In this new paradigm, the number of lots and the scale of manufacture required to allow the evaluation of a new excipient should be scientifically justified. It may be that three lots are adequate under certain circumstances. However, it should be anticipated that more than three lots may be required for some projects. In any case, the excipient

[36] See ICH Q8, *Pharmaceutical Development.* http://www.ich.org/LOB/media/MEDIA1707.pdf

manufacturer should plan to have available at least three lots manufactured at a scale that adequately represents the final manufacturing scale for initial customer trials.

Preparation of distinct lots of excipient should be part of the marketing plan for the introduction of the excipient to the pharmaceutical market. For batch processes, there is not usually an issue with defining what constitutes a discrete batch. However, where continuous processing is used, what constitutes distinct lots can be open to interpretation. Careful consideration should be given to the manufacture of the representative lots that should wherever possible, encompass the full range of acceptable material within the process capability.

3.5 Customer Feedback

Often the customer will commence trials upon the satisfactory completion of the technical inquiry and evaluation by their pharmaceutical development personnel. Feedback from these trials **<1.28>** may identify the need to change the manufacturing process and/or the production or sales specification for the excipient. This may lead to an iterative process of additional customer trials followed by process modifications. Customer feedback can also identify the need for changes in the packaging and or labeling of the excipient **<1.29>**.

If the customer trials are satisfactory, the specifications should be finalized. If the trials are unsatisfactory and specifications need to be revised, then additional samples should be provided to the customer **<1.27>**, along with the revised sales specification, **<1.23>** and with a request for their feedback <**1.28>**.

Once the customer feedback is satisfactory and no further changes in the specifications are indicated, a Quality Agreement Documentation Package should be developed **<1.30>**. The Quality Agreement Documentation Package should contain the Sales Specification, Certificate of Analysis (COA), technical literature (3.4), sampling guidelines (3.4.1), and Excipient Information Package (3.4) which includes stability/retest and expiry information (2.5.1). The COA format and content should be established as described in the IPEC-Americas *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*[28].

3.6 Post Product Launch

Often an excipient product is launched with only a small number of lots produced **<1.31>**. As the manufacturer gains production experience, their ability to produce conforming material increases. Thus, the manufacturer should reevaluate the process capability after approximately 10 lots and again after about 30 lots **<1.32>**, using this information to adjust the Quality Agreement Documentation Package, specification etc. accordingly **<1.33>**. It is desirable for there to be an ongoing assessment of process capability.

3.7 Confidential Information

As noted in 2.3.5 (Drug Master Files), formulators require detailed manufacturing and quality information from the excipient manufacturer for inclusion in their drug registration documentation. Excipient manufacturers often consider some of this information to be confidential. Therefore the excipient manufacturer should consider how this confidential information will be made available for regulatory review**<1.34>**. There are essentially two possible ways to provide this data to the regulatory agencies:

- the first is to provide the detailed data to the dosage form manufacturer directly after they have agreed to keep the subject information confidential **<1.35>**, and
- the other is to make a regulatory submission where a suitable system exists (see 2.3.5 e.g., Drug Master Files in the U.S., Japan and Canada and CEP in Europe) **<1.36>**

It should be noted that for countries that have a Mutual Recognition Agreement with the European Union, reference to the CEP may be made in regulatory filings.

The subject of confidentiality agreements is normally addressed by the legal department of both parties and will not be further addressed in this guide.

4. ASSESSMENT, SELECTION AND SPECIFICATION PROCESS

4.1 Project Initiation

The excipient user will typically initiate a formulation project when they have identified a business opportunity that requires formulation design and development. Such needs could include a new active pharmaceutical ingredient (API), reformulation of an existing product, a formulation for a product line extension, development of a generic equivalent, or identification of an alternative supplier for an existing grade of a pharmaceutical excipient **<4.1>**. The type of project will determine the composition of the project team with the objective of developing the new drug or approving a new supplier.

4.2 New Formulation Development Projects

For new formulation development projects, the project is often initiated by forming a project team with the objective of developing the new drug product. The project team will have responsibility for defining the business opportunity for a marketing application for the intended therapeutic use **<4.2>**. The first decision prior to finalizing the team is whether the project is a drug or formulation development project <**4.3>**. If it is not either of these, then the project involves the selection of an alternative supplier (see Section 4.3)

With the business opportunity identified, the project team is formed and identifies route of administration, dosage form, and target market taking into account the difference in the various geographical regions **<4.4>**. Once the route of administration is decided, the team can then determine the various strengths for formulation. At this stage the project team should carefully assess formulation constraints and opportunities that could impact the quality and performance of the product at later stages. Quality by Design principles should be applied as early in the process as possible.[36]

The project is assigned to a formulation scientist (or team) who is tasked to identify the functional requirements necessary to incorporate the API in the dosage form so as to deliver the API to the patient with the desired therapeutic effect **<4.5>**. Excipients will be expected to provide various functions in the dosage form or it's processing, including, but not limited to:

- Binder
- Compression Aid
- Disintegrant
- Color/Flavor
- Filler
- Sweetener
- Lubricant
- Preservative
- Glidant
- Suspending/Dispersing Agent
- Humectant
- Buffer
- Coating/Film Former
- Identity through printing with ink
- Release Modifier
- Adhesive
- Penetrant
- Vehicle
- Thickener

- Solvation

The use of combinations of excipients in formulations is common since typically no one excipient can provide the complete range of functions necessary to produce the desired dosage form.

Excipients:

- "aid in the processing of the drug delivery system during its manufacture,
- protect, support or enhance stability, bioavailability or patient acceptability,
- assist in product identification,
- enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use."[38]

The use of excipients of multiple functionality in the formulation may result in simplification of the drug formulation design stage since there are fewer excipient suppliers to assess and monitor. The use of fewer excipients may simplify the manufacturing process at the small scale. However, scale up to commercial manufacture may require additional excipients not required in the initial formulation design studies.

4.2.1 Selecting the Excipient

Once the formulation team has identified the excipient functionalities that are needed for the dosage form, they will then develop a list of candidate excipients that meet the project requirements (functionality, etc.) **<4.6>**. The list will be developed from various sources such as the company formulary of excipient ingredients, excipient manufacturers' literature, and technical articles. At this stage, it would be expected that for each desired function, the list contains multiple excipients.

There are several benefits in working with an excipient that has been used by the company in other products. Knowledge will have been gained about the sampling and testing of the excipient for incoming Quality Control approval. The company will have experience with handling the excipient in a safe manner and minimizing the risk of cross contamination. The proper storage conditions for the excipient will also have been established, as well as the retest interval for the excipient. Finally there will often be information related to the cleaning of utensils and equipment after their use with the excipient.

Once the list of excipients has been assembled, the formulator will determine those most appropriate for use with the particular API. Final excipient selection will include an assessment of their prior use within the company **<4.7>**, and could include:

- Name of approved suppliers,
- Identity of the dosage forms where the excipient has been used,
- Functionality the excipient provides to the dosage form,
- Excipient use level in the dosage form,
- Number of years the supplier has been providing the excipient, and
- Performance history of the excipient supplier.

Other factors to consider include:

- Confidential Disclosure Agreement (CDA),
- Price,
- Manufacturing capacity,
- Supply chain,
- Special requirements, such as minimum order quantity or lead time,
- Packaging available,

[38] The Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients*, 2006, p. 3

- Technical competence,
- Quality Assurance systems,
- GMP conformance,
- Audit findings, and
- Source (site of manufacture)

The information gathered for each candidate excipient is used as a preliminary screen to rank the excipients in order of desirability for use in the formulation. The preferred candidate excipients should be compatible with the API[39], and be considered capable of providing the desired functionality at an acceptable use level.

Excipient compatibility studies are conducted at elevated temperatures so as to get quicker indications of physical and chemical interactions with the API. Such interactions may adversely affect the stability or manufacturability of the drug product. Examples of such incompatibilities are:

- Detrimental physical interactions exemplified by binding of the API to the excipient so as to make it unavailable to the patient;
- Interaction between the API and excipient such that the integrity of the API cannot be maintained and an adequate product shelf-life cannot be achieved,
- Detrimental physical interactions that may result in inadequate ability to manufacture the dosage form,
- Compromised performance of the finished product, and
- Interference with the ability to measure the presence of the API in the dosage form.

Chemical interactions generally result in new chemical entities that are usually classified as degradants. If there is no alternative excipient, these degradants must be characterized and evaluated for safety. Where appropriate, limits are assigned to the degradant.

4.2.2 Selecting the Supplier

If it is determined that there are no candidate excipients to provide the desired functionality that have a prior use within the company, then other candidate excipients will be considered **<4.8>**.

Where the candidate excipient has no history of use at the drug manufacturer, the purchasing department will usually be asked to obtain certain information from each supplier of the excipient **<4.9>**. This information may include, but is not limited to the following:

- Excipient Information Package (EIP)[34] from the manufacturer and where appropriate, the distributor. This document would include:
  - The supplier’s commitment to conforming to appropriate excipient GMP requirements,
  - Characterization of the composition of the excipient,
  - Regulatory information,
  - Description of the excipient manufacturing process and facility,
  - Site and supply chain security measures, and
  - BSE/ TSE and allergen information/certifications.
- Technical information supporting the functional performance of the excipient. Such information may include:

[39] Moreton, RC, Excipient Interactions, in Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, edited by Katdare, A and Chaubal, MV, (EDs), Informa Healthcare, New York, 2006, 93-108

- Data showing the performance of the excipient in achieving the desired functionality in model formulations and
- Studies showing the stability of the excipient under model drug product processing conditions.

- Understanding the origin and handling of excipient samples
- Understanding the full supply and distribution chain[2], and
- Pricing and availability at the intended manufacturing site

Experience from working with previously known excipient suppliers is a benefit since the company will have had experience with:

- Supplier's order entry process,
- Delivery performance,
- Certificate of Analysis (COA),
- Suitability of information (e.g. conformance to IPEC guidelines[28, 40]),
- Reliability of the supplier's measurements,
- Packaging,
- Labeling,
- Tamper evident seals,
- Supply chain security measures,
- Conformance to appropriate GMPs, including prior audit history,
- Established supplier profile in the organization, e.g.
  - minimum order quantity,
  - order lead time, payment terms, etc,
  - delivery performance, ability to meet delivery requirements, and
- Reliability of the supplier's measurements reported on the COA.

Such factors may allow the excipient user to go to reduced testing of the incoming excipient more quickly, where justifiable.

Previously qualified suppliers should have been audited by either the user or a suitable third party and should be on a re-audit schedule. IPEC has issued a guideline suitable for conducting audits for conformance to IPEC-PQG excipient GMP requirements[41].

For new suppliers all these issues would need to be addressed as part of supplier qualification, a process that is likely to be undertaken in parallel with the evaluation of the excipient in the intended formulation.

Users should generate audit information through site visits, either using their own audit resources or qualified third party audit providers, for all excipients and their supply chain. Questionnaires should not be used as a substitute for on-site assessment. The user should evaluate this audit information (audit report and site response) to confirm the suitability of the site Quality System and excipient quality for the intended purpose.

The project is now ready to proceed to the suitability assessment step. The candidate excipients are evaluated for their compatibility with the API and therefore samples of the candidate excipient are needed. If the excipient has a history of prior use within the company, samples are usually available or will be requested **<4.10>**. For those excipients not in the company formulary, once the information from the supplier has been reviewed and the supplier has been found to be conditionally acceptable, the formulator requests

[40] IPEC-Americas *Significant Change Guide*, 2005
[41] *The Joint IPEC-PQG Good Manufacturing Practices Audit Guide for Pharmaceutical Excipients 2007*

samples of the candidate excipient. As noted in the Phase 1 portion of this guide, the formulator will need samples representative of the typical commercial excipient.

With samples of the excipient on-hand, assessment of the compatibility of the excipient with the Active Pharmaceutical Ingredient can proceed **<4.11>.**

At this stage of the drug development process, it is critical to inform the excipient supplier, who should then inform the manufacturer as appropriate, that their excipient is being considered for use in a new drug application **<4.12>**. There is considerable benefit to the excipient user in providing as much information as possible about the new drug application. The excipient supplier may have the expertise to:

- Acknowledge the excipient is suitable for the intended route of administration and geographical region,
- Assure the excipient is available in the quantities anticipated,
- Confirm the excipient is stable under the expected processing conditions,
- Provide information on the excipient composition profile[42] to the user, where appropriate, and
- If possible, discuss the reactivity of the excipient to provide information useful to assessing excipient compatibility with the API and other ingredients, etc.

The technical information assembled is used to assess the appropriateness of the excipient for the intended use **<4.13>**. The formulation team would consider all the information available from the **pre-formulation** assessment to confirm that the excipient remains a viable candidate for inclusion in the drug product.

4.2.3 Regulatory Assessment

While the formulator evaluates the sample of the excipient, personnel with appropriate excipient regulatory expertise confirm that the excipient is acceptable for use in the formulation**<4.14>**. This will involve an assessment of the excipient regulatory status in the intended markets. This assessment should confirm the excipient is permitted in the target dosage form or route of administration, and that the expected quantity of excipient to be used in the new drug product is within the maximum quantity previously approved in such applications <**4.15>**. Otherwise the formulator can expect the Regulatory Authorities to request additional safety data.

In conjunction with the excipient supplier communication **<4.12>**, the regulatory department would want to know how the excipient manufacturer would convey pertinent information regarding Chemistry, Manufacturing, and Controls to the regulatory agencies. In countries where an excipient Drug Master File (DMF) system is available and the excipient manufacturer has filed a DMF, the excipient manufacturer can then inform the regulatory agency via an appropriate DMF reference letter that allows the agency access to view the DMF in response to a specified drug filing by the pharmaceutical manufacturer. Where the excipient manufacturer has not filed a DMF with the regulatory authority or in markets where an excipient DMF system is not available, the user can require a commitment from the excipient manufacturer to supply appropriate information under a confidentiality agreement. Whether a DMF has been filed or not, the excipient manufacturer should be prepared to address requests from the drug manufacturer for additional information. In the United States, a DMF is not necessary for excipients complying with a monograph in the *USP-NF*; however, many excipient manufacturers do maintain DMFs for their compendial excipients for other reasons.

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[42] IPEC Excipient Composition Guide (in development)

In Europe a supplier can apply for a European Certificate of Suitability (CEP) from the European Directorate for the Quality of Medicines (EDQM) where there is a monograph in the European Pharmacopoeia. The CEP confirms that the European Pharmacopoeia monograph is adequate to control the excipient. Where a CEP has been issued, this helps to confirm that the excipient is suitable for use in the European region and serves the same purpose to suppliers and users as an U.S. DMF. For those materials for which BSE/TSE precautions are required, a special CEP is available and this is applicable to any excipient, regardless of whether or not it has a monograph in the European Pharmacopoeia.

At this stage of the drug development process, the formulation team would assemble all of the information for review **<4.13>** to confirm that it is appropriate to proceed with formulation development using the candidate excipient **<4.16>**. This review would be both a technical (including pre-formulation **<4.17>**) and regulatory assessment to show that the formulation would provide the intended therapeutic effect and would be likely to receive regulatory approval. With positive indications for both aspects of the assessment, the drug manufacturer would develop a list of preferred excipients for use in the desired formulation **<4.18>**. Where the assessment indicates an excipient in the formulation may not provide the desired performance or may prove to be incompatible, the formulation work would revert to a review of other excipients available **<4.7>**. If no other excipients are suitable, then the formulator proceeds to identify potential excipients not already in the formulary **<4.8>**.

4.2.4 Refining the Excipient List

At this stage in the formulation development process, if no excipients have been identified that provide the desired functionality in the formulation, or if technical and regulatory problems are identified; the formulation team should re-evaluate the feasibility of the project scope by referring back to **<4.2>** or **<4.16>** as appropriate. Where the list contains several excipients that can provide the desired functionality, the list of excipients should be refined to develop a short list of excipients **<4.19>**.

Where the excipient list contains multiple items, the formulator or team would prioritize and screen the excipients using the information available. The evaluation criteria may include at this stage **<4.20>**, excipient:

- Stability,
- Storage conditions,
- Supplier testing to user specifications,
- User confirmation of supplier COA,
- Global regulatory acceptability,
- Availability of supply local to the proposed drug manufacturing facilities (e.g. import restrictions),
- Supplier Quality Assessment information,
- Supplier GMP conformance (based upon qualified audit information),
- Labeling issues,
- Issues involving tamper-evident seals,
- Supplier agreement to notify in the event of significant change,
- Regulatory constraints, and
- Cost considerations.

A comparison of the listed excipients using the above criteria would be expected to identify the preferred excipient(s).

A business decision is often made concerning the need for multiple suppliers of the excipient **<4.21>**. Where more than one supplier is desired, the formulator would determine

if samples from alternative suppliers are available for evaluation. If suitable samples are unavailable, the formulator would request samples.

The final step at this stage of the dosage development project is to perform a risk assessment to select the excipients and processing method with the best likelihood of success for the project **<4.22>**. This assessment should include a review of the results from either an on-site or qualified third-party audit, including distributors. If other assessment techniques are used, they should be justified[43]. If the likelihood of success is unacceptably low, the project would ordinarily either be cancelled, or the project's scope would be changed **<4.23>**.

4.2.5 Formulation Design, Development, and Optimization

Initial formulation and process design studies may cover a broad range of excipients used in a number of trial formulations **<4.24>**. At this stage the emphasis is to find at least one formulation that meets the target profile. Once suitable formulations have been identified and assessed for potential use, the project can progress to formulation and process optimization.

QbD is an approach to designing and developing formulations and manufacturing processes to provide optimum product quality. QbD facilitates the understanding and control of the formulation and manufacturing process variables that affect the quality of the drug product. QbD begins with the pre-formulation assessment (e.g., excipient compatibility), and continues with the development of a drug formulation having the required performance characteristics to meet the expectations of the regulatory agency, patient or caregiver. QbD typically leads to the following stages of the development process:

1. Definition of the target product quality profile to meet expectations
2. Design and development of product and manufacturing process to meet the target product quality profile
3. Identification and understanding of:
    a. critical raw material attributes,
    b. critical process parameters, and
    c. sources of variability.
4. Monitoring of the process and adjustment within normal variation of process variables (as identified in 3 above) to produce consistent product quality, leading to appropriate in-process controls.

QbD properly executed leads to an understanding of the Design Space, which is the range of input variables within which the process can operate and still produce conforming drug product. These input variables include raw materials as well as equipment operating parameters. The Design Space may be determined through such techniques as Design of Experiments (DoE)[33].

The process for finalizing the drug formulation begins with a review of the decision whether alternative suppliers are required or that single sourcing is acceptable **<4.25>**. If the decision is made to seek alternative suppliers, then the process returns to identifying suppliers and requesting samples **<4.34>** (see Section 4.3).

In either event, samples are obtained from multiple lots of the excipient from the candidate suppliers **<4.26>**. The pharmaceutical manufacturer prefers samples that represent the range of specification properties and performance expectations that result from the excipient manufacturing process capability. While desirable, it may not be possible for the excipient

[43] GMP paper audits or EIP Site Quality Overviews alone are insufficient for this purpose.

manufacturer to provide such samples, particularly with excipients manufactured by continuous processing, but also sometimes with excipients produced using batch processing. Other options for such investigations can be considered; for example the use of samples from other appropriate pharmaceutical grades, or even non-pharmaceutical grade samples at the user's discretion. Nevertheless, multiple lot samples should represent current excipient manufacturing process variability to the extent possible. To facilitate provision of proper samples that demonstrate excipient functionality and variability, intercompany technical discussions should be held.

With proper samples and a well designed DoE approach, a robust formulation can be developed that will provide an acceptable drug product as long as the excipients used conform to their sales specification. Representative samples from the excipient lots are taken and tested for conformance to the excipient sales specification and where applicable, the excipient compendial monograph. The multiple excipient lots will be tested using methods intended to confirm that the excipient will provide the desired performance in the formulation.

When the testing of the multiple lots of excipient meets requirements, the excipient will be available for formulation work. Once all excipients and the API have been identified, and feasibility of the formulation confirmed, formulation development and process optimization will be initiated **<4.27>**. In addition, two further simultaneous activities will be undertaken: the evaluation of excipient test methods, the frequency of testing, and specifications **<4.28>**; and the identification of performance indicating requirements and related test limits **<4.29>**. As performance indicating requirements and related test methods are identified, if these are different from those already supplied by the excipient manufacturer, they should be communicated to the supplier. Evaluation of the excipient manufacturer's ability to test against these requirements, and the frequency with which they can do so, should be understood **<4.28>**.

Information should flow between technical personnel at the supplier and the user. The evaluation of supplier test methodology can include discussions with the supplier to gain an understanding of their release testing and validation activities The supplier should disclose sufficient details concerning the Chemistry, Manufacturing, and Controls (CMC) relating to the excipient so that the drug manufacturer can assess the quality and consistency of the excipient, and to enable development of a pharmaceutical product using QbD concepts. The dosage form manufacturer should disclose sufficient details of the dosage form so that the excipient supplier can confirm the selected grade is appropriate for the intended route of administration and geographical region. The outcome of the discussion between supplier and user should allow the updating of the specification for the excipient including any additional requirements **<4.30>.** Confirmatory testing is performed on multiple lots to assure that the proposed tests can be performed and the limits can be met **<4.31>**. This information is used to develop the draft excipient specification for the intended application **<4.32>**. The draft specification is then communicated to the excipient supplier for review (see Phase 3). Any refinement of performance requirements or specifications **<4.33>** should result in modification to test limits **<4.29>.**

4.3 Alternative Excipient Source Projects

The specification and performance of the excipient will already have been defined in this case and so the requirement is simply to find an alternative that provides the same functionality.

Having defined the project as not being a 'new formulation development' project **<4.3>**, the project should be confirmed as an 'alternate source' project.

‘Alternative source’ projects may be motivated by a number of reasons:
- Cost savings,
- Addition of further suppliers,
- The existing supplier may no longer be able to supply the material, or
- Business continuity planning:
  - contingency plan,
  - reduce reliance on a single source for capacity purposes.

Typically, such projects will be undertaken in a commercial manufacturing setting, rather than R&D. A project team would be organized, and the project goals defined. The team would be comprised of representatives from several functions, but as a minimum should include representatives from: Manufacturing, Production Planning, Quality Assurance, Purchasing, and Technical Services, or Production Support. Representatives from other disciplines may also be included such as Regulatory Affairs, R&D, and Finance.

An evaluation should be performed to determine the potential **interchangeability** for the existing excipient. Based on the results of the evaluation, a decision on the suitability of the supplier(s) would be made **<4.34>**. Where there are suitable alternatives, those suppliers would be contacted **<4.35>**.

An evaluation of potential alternative suppliers is performed using criteria **<4.36>** including:
- Competitive pricing,
- Production capacity,
- Suitability of their supply chain,
- User specified requirements,
- Performance history as a supplier to the company and the pharmaceutical industry,
- Suitability of excipient packaging,
- Potential for cost saving,
- Technical competence and support available,
- Appropriateness of the quality system, and
- Conformance of the site to GMP requirements.

If there are discrepancies, or an ideal supplier cannot be found (i.e. meeting <u>all</u> the preferred criteria for interchangeability, as defined by the Project Team), an assessment of the likelihood of satisfactorily resolving the issues would be made **<4.37>**. This assessment would necessarily include discussions and negotiations with the potential supplier(s) **<4.38>**. If the discrepancies can be resolved, the progression of the project will depend on the willingness of the excipient manufacturer to implement the necessary changes **<4.39>**. If the supplier is unwilling or unable to implement the changes, the user company has the option to either seek another supplier **<4.40>**, to terminate the alternative supplier project, or explore other options **<4.41>** (as discussed in Phase 3). If the supplier will implement the proposed changes, the project progression could/would be dependent on the final implementation of the changes **<4.42>** followed by another evaluation of the supplier **<4.36>**.

Assuming the evaluation ultimately identifies an acceptable alternative supplier, the next stage would be to obtain appropriate samples of the excipient from that supplier **<4.43>**, as necessary. This may require sample from several lots of the excipient covering the range of material characteristics seen with the particular grade (see Phase 1, Section 3.4.1).

Once the appropriate samples are available, the project would progress through:
- Laboratory/small scale evaluations (including excipient characterization) **<4.44>**
- Pilot scale investigations (studies) **<4.46>**

- Pivotal scale investigations (studies) **<4.49>**
- Commercial scale investigations (studies) **<4.51>**, and
- Validation and commercial production (studies) **<4.53>.**

This list of activities at the different scales of manufacture listed above is not intended to be followed rigorously. Depending on the nature of the excipient and the type of product being considered, it may be possible to skip e.g., the pilot scale investigations and/or the pivotal scale investigations.

Before transitioning from one stage to the next, the results from the current stage would be assessed **<4.45>**, **<4.48>**, **<4.50>** and **<4.52>**. If the assessment is satisfactory, the project would move to the next stage as designated by the Project Team. If there are any issues, the progress and the project would need to be reassessed **<4.47>**.

In 'alternative source' projects, the ideal is to identify the source of an excipient grade that is functionally equivalent in all respects to the original source material (interchangeable). However, this may not be entirely possible, and 'functional equivalence' may mean addressing the question, "What changes in the unit processes are required to produce an equivalent drug product using this source of the new excipient?"

Since these projects typically concern commercial products, the U.S. FDA's SUPAC Guidance (Scale-up and Post Approval Change) will apply to any products manufactured for the U.S. market. In Europe, the Variations Regulation will apply. There may be equivalent rules in other regions. The type of product (immediate release vs. modified release), the biopharmaceutical classification of the API (Biopharmaceutical Classification System Class 1 vs. Classes 2, 3, and 4), and the criticality of the excipient (particularly for modified release products) will all influence the sophistication of the data required to support the regulatory filing of the change. Such data may include, but is not limited to:

- Stability,
- Dissolution,
- Bioequivalence requirements, and
- Revalidation of
  - Manufacturing and
  - Analytical methods.

For modified release products, particularly with a release controlling excipient, it is likely that the pharmaceutical manufacturer would consider a bioequivalence study at least at the pivotal scale, even if they have a good *in-vitro-in-vivo* correlation.

Assuming the project is successful, there will be a need to formally negotiate a Supply Agreement (see 4.4 below). The precise timing will depend on the organizations involved. However, it is likely to be before the commercial scale investigations **<4.51>**. The negotiation process is covered in Section 5 (Phase 3) of this Guideline.

4.4 Negotiation Process Impact

It is recognized that the negotiation process discussed in Phase 3 may require the re-assessment of performance requirements and specifications **<4.32>** or **<4.33>.** When the need for additional refinement of performance requirements and specifications is indicated, the process will revert back to **<4.29>** for the further identification of performance indicating requirements and test limits.

5. NEGOTIATION PROCESS

The negotiation process may be invoked for a variety of reasons including:

- New material,
- New grade,
- Updated specification,
- Revision or renewal of an existing Quality Agreement,
- Move to an alternative supplier, and
- Disagreement related to issues discussed in Phases 1 or 2.

Apart from quality of material matters which have been extensively covered in Phase 1 and Phase 2 of this document, the following quality of service issues should also be communicated by the excipient user and evaluated by the excipient supplier before entering into a supply agreement.

Typically, negotiations will be formally initiated when the excipient user issues a Request for Pricing (RfP) or solicits a 'bid' or 'quote'.

5.1 Review of Excipient User Requirements

The excipient user initiates the negotiation process by providing written copies of their excipient specification and any other requirements to the manufacturer or distributor (supplier) **<5.1>**. The specifications for the excipient may stipulate either compendial grade, where available and suitable, or provide specification parameters, test methods, and acceptance criteria for the specified properties. It is also appropriate to provide the supplier with any other atypical or important requirements including:

- Minimum order size and number of lots per receipt,
- Remaining shelf life or reevaluation interval upon receipt,
- Special packaging,
- Special labeling,
- Special shipping, or
- Specified manufacturing facility.

The supplier reviews the proposed specifications and other requirements to ascertain their ability to meet customer expectations using their standard excipient grade **<5.2>**. An objective technical review should be conducted by such groups as the Quality Unit, Regulatory, Manufacturing, Technical Services, etc. Sales or Marketing should not perform this review without subsequent review by a technical department, since the former have a vested interest in making the sale.

The evaluation of the excipient specifications by the supplier should include review of:

- Specified parameters: to confirm that test data are available,
- Test methods for those parameters: to confirm that those tests can be performed or that suitable alternatives are available,
- Test results: for the specified parameters,
- Frequency of testing, and
- Conformance statements: usually relating to supply of compendial excipient.

The reviewer can then determine the manufacturer's ability to reliably supply excipient to the customer's specification.

There is agreement on the specifications when the specification proposed by the customer is congruent with the excipient manufacturer's specification. Where there are differences in the customer requirements and the supplier's standard product, the manufacturer should review their process capabilities to determine the feasibility of meeting the unresolved customer requirement.

Caution should be exercised in agreeing to meet a customer specification where the known process capability studies indicate there is a low likelihood of meeting the specification.

A similar review of other customer requirements should be conducted **<5.3>**. It is important for the supplier to involve parties with direct knowledge of the ability to meet specified requirements. By involving such knowledgeable personnel there is increased assurance the supplier will be able to routinely meet customer requirements. Examples of such requirements are requests for special packaging, label content, palletizing, floor versus pallet loading, and pallet construction.

Agreement on specifications should be formally documented **<5.4>**. A written agreement should be established between the customer and supplier. Where a distributor is used, there must be a process between the distributor and excipient manufacturer to assure the specifications are reviewed and accepted by the manufacturer[2]. It is critical that the specifications are reviewed and approved by the appropriate technical personnel at the excipient manufacturer to acknowledge agreement.

If the excipient manufacturer agrees to meet the customer specification and specified requirements, the supplier would provide pricing to the customer **<5.5>**. The pricing should include the cost of supply chain issues such as **<5.6>**:

1. Product ownership: where the supplier is expected to retain ownership of the excipient even after the excipient has left the manufacturing site (e.g., consignment stock).
2. Packaging and Labeling:
    a. Additional label content such as customer specified product coding and barcodes,
    b. Use of unique packaging components such as specified plastic bags and container/closure materials, and
    c. Special size packages or net weight such as bulk containers.
3. Shipping:
    a. Special configurations:
        - palletizing and shrink-wrap,
        - container floor loading, or
        - pallet configurations and materials of construction.
    b. Minimum order quantity,
    c. Lead time: to assure conforming excipient is available to ship,
    d. General carriers, specified carriers, or customer pickup,
    e. Multiple lot versus single lot shipments,
    f. Pre- and Co-shipment samples (if mutually agreed) including:
        - how and from where the samples are to be collected (including the sampling plan),
        - the quantity of sample,
        - how the sample is to be packaged,
        - how they are to be shipped,
        - the recipient address, and
        - for pre-shipment samples.
            - when in the order cycle samples should be provided, and
            - whom at the supplier should receive the users approval to ship.

Note: Where the parties agree to such sampling, caution should be exercised to assure that appropriate GMP requirements are met.

5.2 Quality Agreement

It is good practice for the excipient supplier and user to define and enter into a Quality Agreement **<5.7>**[44].

The Quality Agreement may cover the following topics, but the inclusion of these or of other topics is a matter for agreement between the two parties **<5.7>**:

1. Compliance
    - Excipient specifications, including,
        a. Additional functional tests,
        b. Altered ranges of tests already in the excipient suppliers standard specification,
        c. Alternative test methods either for parameters already in the manufacturers' specification or for additional parameters, and
        d. Microbial test limits.
2. Sourcing,
    - BSE/TSE, GMO, allergens, etc. risk assessments,
    - Acceptability (as appropriate) of excipient from multiple manufacturing locations,
    - Restriction, or allowance, of contract operations such as manufacturing; packaging and laboratory testing,
    - Identification of the country of origin and restriction to specified locations,
    - Importation restrictions, and
    - Special certifications such as Kosher or Halal approval.
3. Auditing,
    - The right of the customer to audit supplier's facilities and systems at a mutually agreeable time,
    - Confidentiality agreement as required,
    - User to issue a written report within a specified timeframe, and
    - Supplier to respond to report with a specified timeframe.
4. Notification of changes,
    - Conformance to designated quality system,
    - Conformance to specified compendia such as *USP-NF*, Ph.Eur., and JP, and
    - Disclosure of regulatory agency inspections and findings.
5. Provide an understanding of the intended use including:
    - Route of administration and
    - Geographical region.
6. Communication
    - Nonconformance
        a. Out-of-Specification (OOS),
            - Test results to be investigated and documented according to procedure.
    - Other Quality Issues,
        a. Deviations,
            - Documentation of investigation of significant process deviations.
        b. Complaints,
            - Investigation of complaints involving product quality according to procedure and communication to the customer,
            - Promptly reporting complaints and provision of samples by the customer as appropriate, and
            - Cooperation between both parties in the investigation.
7. Manufacturing, Packaging and Labeling,

[44] IPEC Quality Agreement Guide (in development)

    - Qualification of manufacturing and packaging processes,
    - Validation of cleaning and analytical methods, where appropriate,
    - Sample retention, and
    - Special labeling requirements.
8. Documentation and Records,
    - Certificate of Analysis (COA) to be supplied with each lot,
    - Content of the COA,
    - Additional information to be included on the COA,
    - Use of electronic signatures, and
    - Retention period for applicable records.
9. Storage and Distribution
    - Documentation in support of recommended storage conditions and retest interval,
    - Recommended storage and transportation conditions,
    - Storage and shipment in conformance to recommendations, and
    - Use of reusable shipping containers.
10. Change Control,
    - Handling of change notification such as following the guidance provided by the Significant Change Guide[40].
11. Recalls
    - Prompt notification to the customer by the supplier,
    - Cooperate of both parties in the recall, and
    - Supplier will have a recall procedure that has been demonstrated as effective.

5.3 Modification of Requirements

If the supplier finds they are unable to meet either the customer specification and/or other requirements, the customer should be promptly notified **<5.8>**. The supplier should clearly identify specifications and requirements they cannot achieve and include an explanation as to why **<5.9>**. The customer should review the correspondence and seek to clarify any points as necessary.

Once the customer requirements and supplier capabilities are clearly understood, the parties can determine what concessions can be made that are acceptable to both <**5.10>**. The customer specification would only be modified if the changes are not expected to affect the functionality of the excipient in the intended dosage form.

If the customer is unable to alter the specification or other requirements, they would then inquire as to whether the supplier was in a position to make appropriate changes. If the user and/or the supplier are able to reach agreement on the specification and other requirements **<5.11>**, an agreement to supply excipient is achieved **<5.4>**.

It should be recognized that altering specifications and other requirements can be time consuming. If the change is made by the user, they must ensure that the change will not alter their ability to achieve the desired functionality and reliability of supply. If the supplier makes the change, they must confirm their ability to reliably supply excipient of the specified quality and to the specified requirements. There will often be considerable internal discussion and data evaluation by both the supplier and the user before reaching an appropriate decision.

5.4 Identification of Potential Solutions

Where agreement through modification of specifications and other requirements cannot be readily achieved, then other solutions should be explored **<5.12>**. The supplier will be requested to work with the user to develop a solution **<5.13>**. It should be recognized that the supplier can decide not to work with the user and exercises their option to walk away from the potential business

<5.39>. For technical and/or business reasons they may be unable to agree to the user specification and/or other requirements. In that event, the process then proceeds to section 5.5, Other Approaches.

If the supplier agrees to work with the user, the supplier will assess whether lot selection can meet the user's desired excipient quality **<5.14>**. The supplier identifies inventory that conforms to the user's specification **<5.15>**. This approach is discussed in some detail under Section 5.4.1.

A more suitable solution is custom manufacture, where the supplier either alters the manufacturing process for the excipient to produce the excipient on demand to meet the user specification **<5.31>** or further processes the finished excipient in a custom manufacturing operation **<5.33>**. Further processing may be performed where unique solid state properties such as particle size, particle size distribution, and bulk density are desired.

5.4.1 Lot Selection

Lot selection is the practice of comparing the test results for the material in the supplier's inventory against the user's specification to identify those lots that conform. However, such approaches do not guarantee continuity of supply from the excipient supplier since not every lot may conform. Both parties should ensure that the process capability is sufficient to ensure continued supply in a timely manner.

Lot selection should be the consideration of last resort due to the risks involved, including inhomogeneity, continuity of supply, etc. The agreement to use lot selection should be documented between the parties.

This discussion is meant to alert the user to the many issues that arise from relying on lot selection for conforming excipient. For additional information on these issues, see references under Appendix C Bibliography.

Evaluation of the suitability of lot selection begins with the identification by the customer of the property, measurement method, and acceptance criteria **<5.16>**. The supplier then evaluates the measurement method and their ability to perform the measurement at their manufacturing location or otherwise identifies where the test can be performed **<5.17>**. A potential test location is the user who would then use pre- or co-shipment samples provided by the supplier.

Three important criteria should be met if lot selection is to be used to fulfill the user requirements: intra-lot variability, inter-lot variability, and the stability of the property.

Lot selection should only be used when the excipient manufacturing processes operates in a state of **statistical control**. **Random variation** associated with the property used for lot selection is important to ensuring the sampling plan will adequately protect the customer from receiving a non-conforming lot. With the process in statistical control and displaying random variation, it is possible to gather data for intra-lot variability **<5.18>**. Generally this is accomplished through statistical sampling of a lot so as to show with a high degree of confidence (≥95% Confidence Interval), that the lot is homogenous. This allows for the establishment of a routine lot sampling plan.

Lot selection relies on understanding the variation associated with the property being measured in relation to the required range. As a basis for considering lot selection, it is important to quantify the intra-lot variation of that property. Variation of this property in the excipient results from the variability contributed by both the manufacturing process and the measurement system.

Measurement variation is the result of the variability of the entire system from sampling through testing. It includes such sources of variation as:

- Sampling technique,
- Sample non-uniformity,
- Sample preparation,
- Test equipment,
- Analyst technique, and
- Laboratory conditions.

Variability between the supplier's measurement process and that of the user's measurement process should also be considered. Otherwise there can be a disagreement as to whether the lot meets the requirements.

The second criterion for consideration is inter-lot variability. Sufficient data should be gathered so as to measure the lot to lot variation of the excipient **<5.19>**. Ideally the average value of the data for the property under evaluation will be midway between the specified ranges. Also when this data is plotted, the shape of the histogram should approach a Gaussian Curve (Normal Distribution).

Manufacturing process variation, resulting in lot-to-lot variability, arises from:

- Seasonal impacts due to such changes as:
    - Raw materials,
    - Water quality, and
    - Environmental conditions.
- Effects of process aging such as:
    - Catalyst life,
    - Equipment wear,
    - Filter efficiency, and
    - Equipment cleanliness.
- Operational differences:
    - Equipment,
    - Personnel,
    - Process control, and
    - Raw material through storage and handling.

The final criterion is an assessment of the stability of the excipient **<5.20>** which is an important factor that can affect the decision to provide excipient using lot selection. With a stable excipient **<5.21>** and user concurrence to take inventory that has been held for a prolonged interval, the supplier can set aside sufficient conforming excipient to meet the anticipated needs of the user for an extended period. If the excipient does not possess adequate stability to inventory material from lot selection, the user will need to re-assess their options **<5.23>**. Among the options the user can consider are in-house modification **<5.43>** of the excipient grade that is available (Section 5.5.1) and where this is not feasible, reformulation of the drug product (Section 5.5.2) **<5.44>**.

The process capability of the specified property should be calculated to confirm it is adequate for the purpose of lot selection **<5.22>**.

$$C_{pk} = \text{minimum (USL-Avg or Avg-LSL)}/3\sigma$$

Where USL = Upper Specification Limit,
LSL = Lower Specification Limit,

Avg = Average, and
σ = standard deviation.

It is noted that a process capability (C_{pk}) value of 1.0 indicates that 99.7% of material would meet the specification. Depending on the mutually agreed level of risk, lower process capability can be acceptable. The inherent risks should be thoroughly understood and acknowledged by both the user and supplier.

Once quantified, the variability arising from manufacturing and measurement along with the desired specification range can be used to determine the number of samples that are needed from each lot to assure the entire lot conforms to the user specification[45]. Simply stated, the more variation, whether it arises from manufacturing manifested as lot non-homogeneity or lot-to-lot variation, or the measurement system, the greater the number of samples needed to assure the accuracy of the measurement result, and the subsequent acceptance decision. The determination of the proper number of samples needed to assure the proper accept/reject decision, is determined from the **Operating Characteristic** (OC) curve. This curve of a plot of the probability of acceptance vs. the true lot average demonstrates the proper number of samples to achieve a statistical probability the lot conforms to specification.

Briefly, an OC curve uses the **customer risk** (the risk that nonconforming lots are released as acceptable), the **producer risk**, (the risk that conforming lots are rejected as unacceptable), the specification range, and variation (both manufacturing process and measurement system) and determines the appropriate acceptance sampling plan[46]. It should be noted that the closer the measurement average for the property to the center point of the specified range, the fewer samples that will be needed to achieve a constant level of risk.

The ability of the supplier to reliably provide excipient to the user's specification is dependent upon the quantity of material the user orders versus the quantity of material produced during that time period that meets the user specification. There are many factors to consider but at a minimum, it is desirable for the ratio of production to user order requirements should be at least 3:1; allowing the supplier to select inventory to fill the customer order **<5.24>**. Otherwise the user may find the supplier does not have sufficient conforming material to meet their order quantity and delivery requirements.

Generally lot selection is viable **<5.25> <5.26>** when there is mutual agreement between manufacturer and user concerning:

1. Cost of manufacture provides an adequate profit to the manufacturer at an acceptable cost to the user,
2. The supplier can agree to provide a continuity of supply of conforming excipient.
3. The excipient is stable enough so that the user receives it with sufficient shelf life for use in the manufacture of the pharmaceutical product.
4. The business objectives of both supplier and user have been met.

If there are no agreements on these issues **<5.27>**, then the user will have to re-assess their options **<5.23>**.

With agreement the supplier and user will evaluate the ability of the supplier to test for conformance to the user requirements **<5.28>**. If the supplier is capable of performing the appropriate tests and can provide their results on a Certificate of Analysis (COA), then the

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[45] *Specifications for the Chemical and Process Industries, A Manual for Development and Use*, American Society for Quality, 1996, 61-64.

[46] *Specifications for the Chemical and Process Industries, A Manual for Development and Use*, American Society for Quality, 1996, 75-90.

supplier can implement special inventory management and logistics as necessary **<5.30>**. Otherwise, the user might request that the supplier provide pre-shipment samples so that the user can test and identify those lots that meet user requirements **<5.29>**. The supplier and/or user would then implement appropriate inventory and logistics management.

5.4.2 Manufacture to Order

Where the stability of the excipient is inadequate or where the process capability is insufficient for lot selection **<5.21> <5.22>**, consideration should be given by the excipient supplier to produce the excipient to order **<5.31>**. This often involves careful process monitoring that result in the excipient with the property desired by the user. The excipient is manufactured to fulfill the user order where the user will supply a forecast to the manufacturer with an agreed to lead time **<5.34>**. The manufacturer will then assure there is conforming material in inventory to meet the user demand forecast and there will be an agreement to proceed **<5.27>** between supplier and user.

Where the excipient supplier cannot meet the user requirements by producing the excipient to order, the manufacturer can consider custom manufacturing the excipient **<5.32>**. Otherwise the user will need to reassess their options **<5.23>**.

5.5 Other Approaches

Where the supplier has declined the business **<5.39>**, the user should ascertain if there are any other suppliers capable of providing the excipient quality desired. If there is another supplier **<5.41>**, the user would return to Phase 2 **<4.34>** and evaluate that supplier's excipient. If the user cannot identify another supplier of the excipient, the user might then consider either reformulating the dosage or modifying the excipient quality available in-house to meet the requirements of the formulation.

5.5.1 In-House Processing

If there is no supplier **<5.40>,** the user is left with the option to consider in-house modification of the excipient **<5.42> <5.43>**. This approach is practical in circumstances where certain physical properties of the excipient are desired, such as finer or more uniform particle size for powders and homogeneity of batches for liquids. Improvements to the chemical properties of the excipient that might be feasible include increased purity, removal of a specified impurity or concomitant component, alteration of the excipient pH, or treatment to reduce the excipient activity. Other considerations for in-house processing include modification of moisture content and reduction of bioburden. Finally, the user can purchase a non-pharmaceutical grade of material and under appropriate GMP, can improve the purity of the material so that it now meets the requirements for an excipient ingredient. Such activities should be justified in the regulatory filing.

Where purification of a non-pharmaceutical grade of starting material is conducted, the user should qualify the material and justify the steps used to improve its purity. It is not acceptable to purchase a "technical" grade of material and simply test it to confirm it meets compendial standards. Without production conducted in conformance to appropriate GMP requirements, the material remains unsuitable for use as an excipient.

5.5.2 Reformulate

Where the stability of the excipient is inadequate and where the excipient cannot be made to order, the user will not have an assured supply of excipient that meets their requirements. In that case, the user will be left with no alternative but to reformulate **<5.44>**.

5.5.3 Supplier Custom Manufacture

If lot selection is not viable, then custom manufacture can be considered **<5.33>**. The data from lot selection as discussed in Section 5.4.1 is assessed for intra-lot **<5.18>** and inter-lot **<5.19>** variability. This information is used to make the determination as to whether the process capability is sufficient **<5.22>**. Where process capability is insufficient for manufacture to order (Section 5.4.2), process modifications can be considered **<5.36>** to achieve the desired excipient quality **<5.37>**. If the process can be optimized, then data can be developed to support the new process capability. If process optimization will not achieve the target excipient quality, the user will have to re-assess their options **<5.23>**.

If the modified process shows adequate capability, then consideration can be given to custom manufacture of the excipient **<5.35>**. Examples where custom manufacture might be indicated were discussed under Section 5.5.1, In-House Processing. The important difference is that the manufacturing improvement in custom manufacture occurs at an excipient manufacturing facility whereas in-house processing occurs under the direction of the user.

If custom manufacture is viable and the product is used exclusively for the user **<5.38>**, there is an agreement to proceed **<5.27>**. Where the excipient is not produced exclusively for the user and there is still an agreement with the user to proceed, the process returns to Phase 1 for the introduction of a new excipient grade.

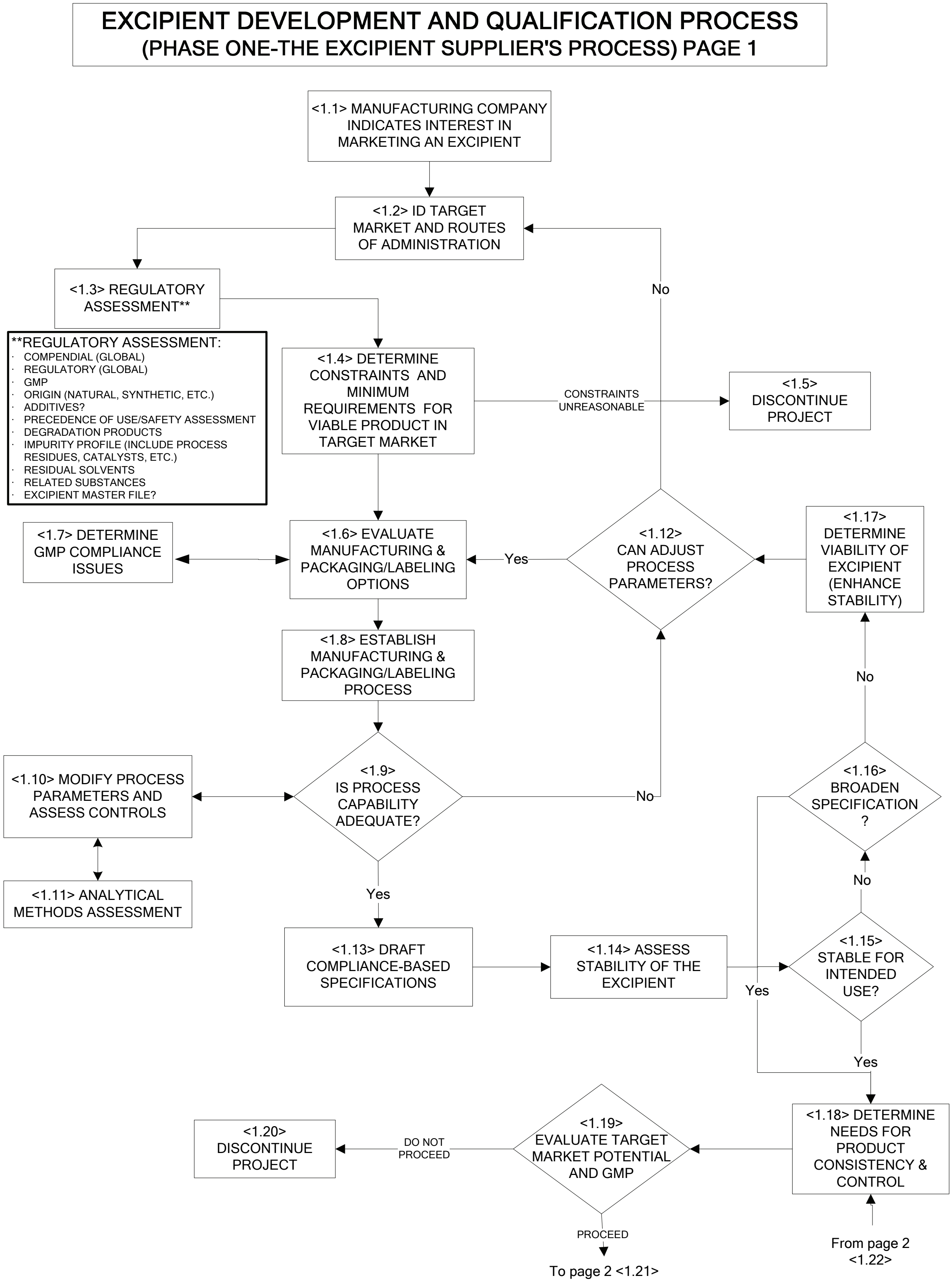
5.6 Concluding Agreements

Where there is mutual agreement to use a special excipient grade to meet the user specification, it is important for the user to supply a forecast to provide the supplier with adequate lead time **<5.34>**. The accuracy of the user forecast and the supplier's desire for lead time are negotiated prior to reaching final agreement.

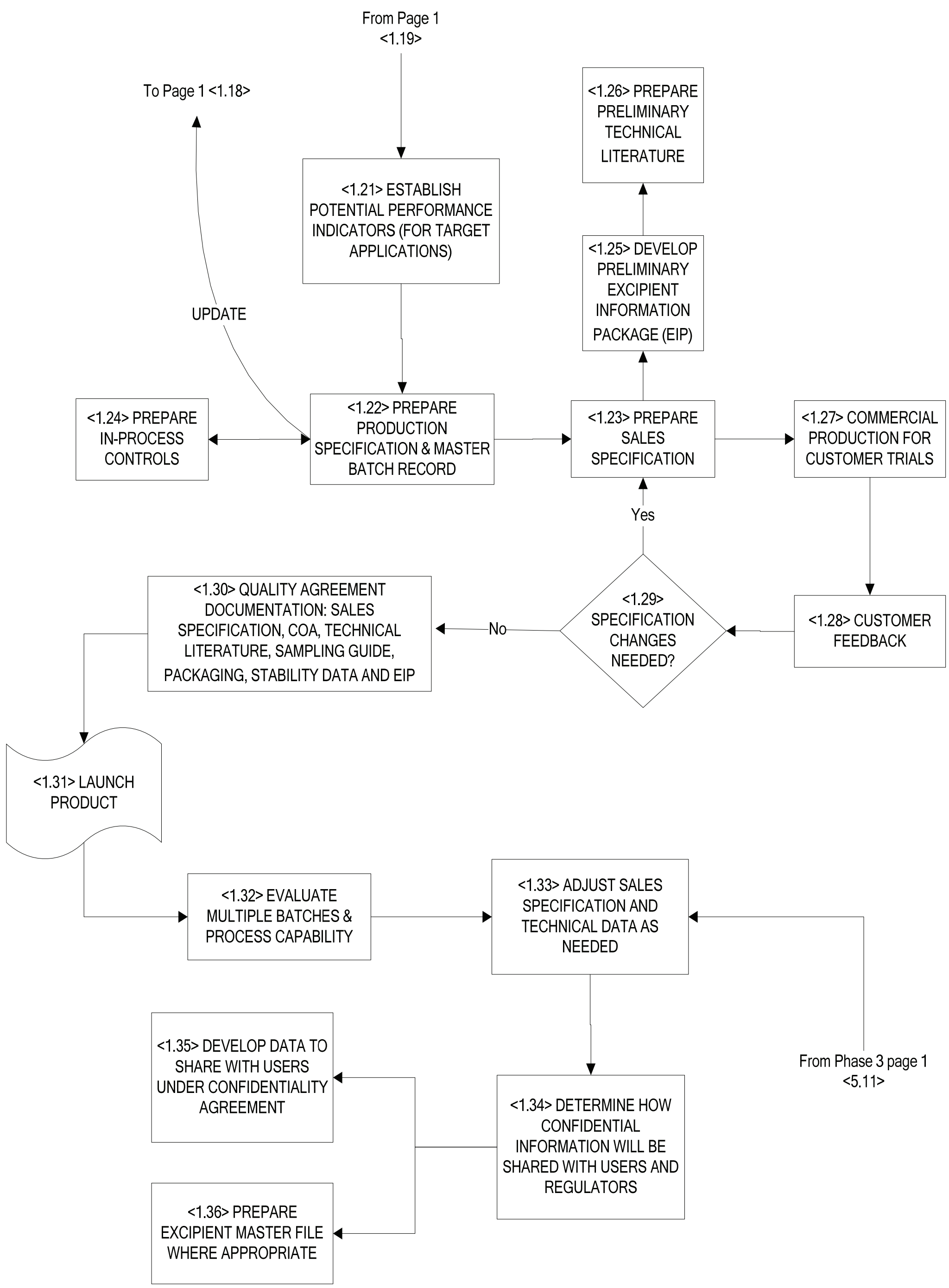
With agreement to proceed, the supplier approves the user specification and other requirements. If the user requires pre-shipment samples, the supplier makes arrangements to provide them <**5.29>** (see Section 5.1).

If the agreement requires lot selection, the supplier and/or user should implement inventory management procedures to assure there is appropriate inventory to meet the user forecast **<5.30>** within the desired lead time <**5.34>**.

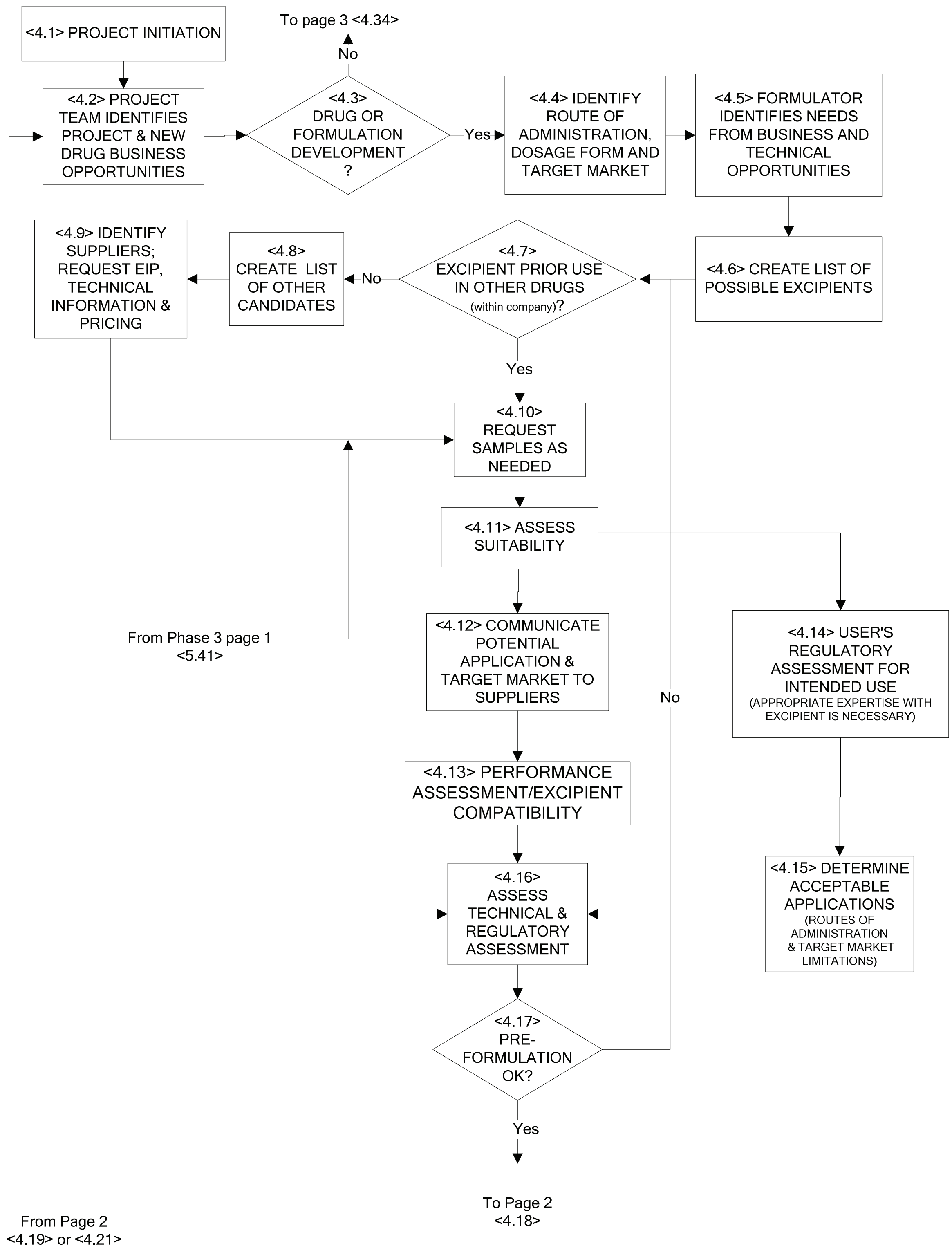
APPENDIX A: FLOW DIAGRAMS



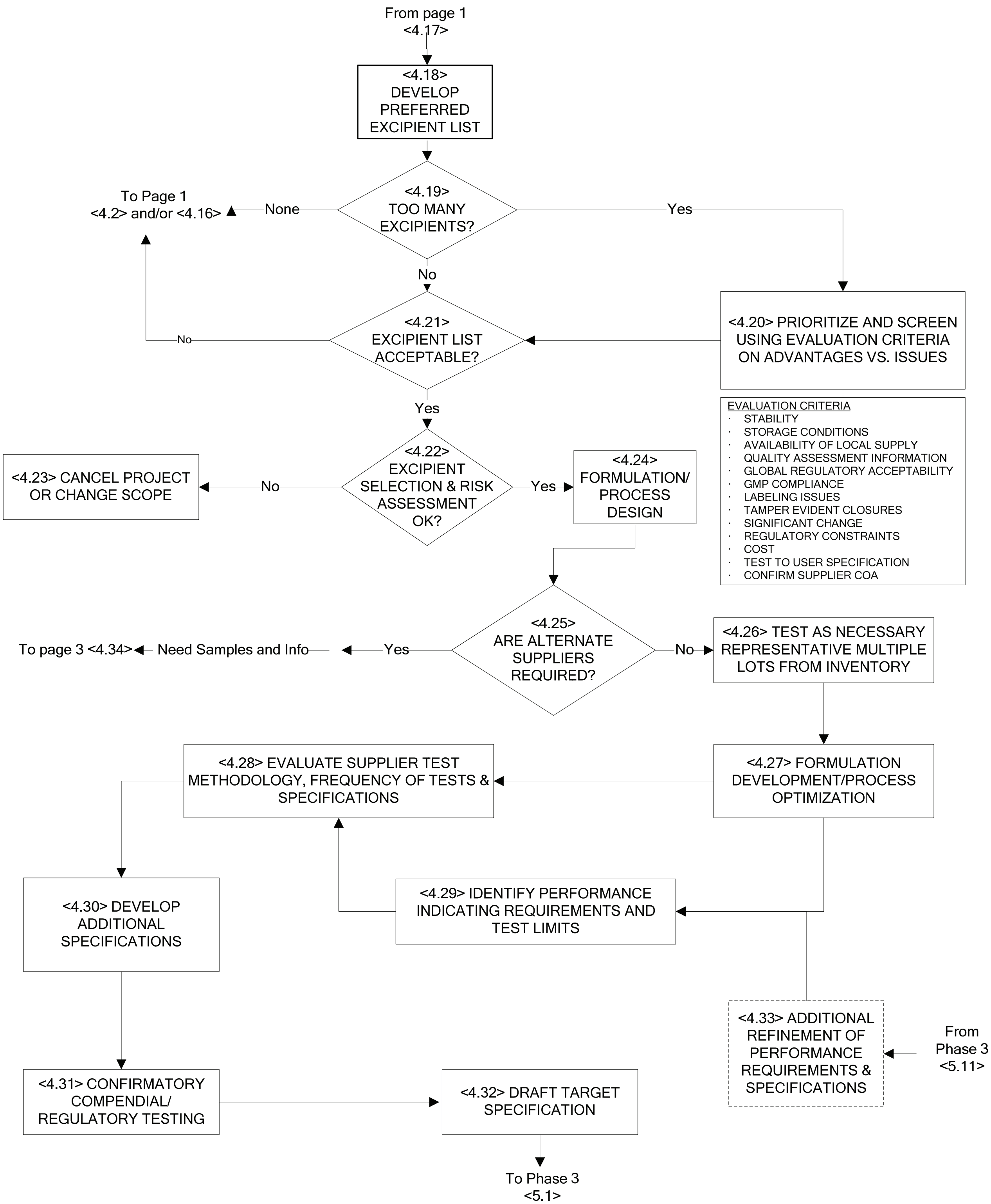
EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE ONE-THE EXCIPIENT SUPPLIER'S PROCESS) PAGE 2



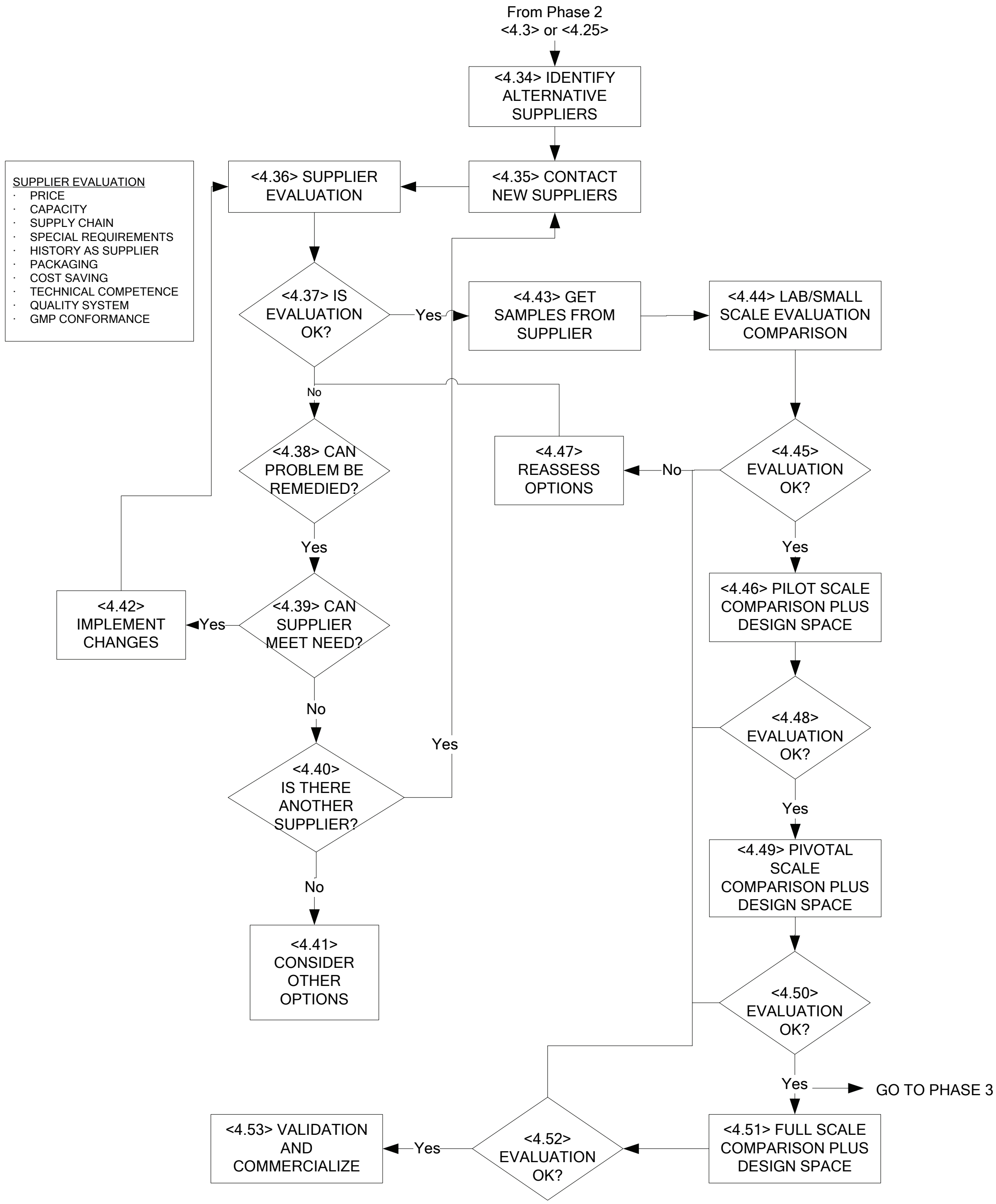
EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE TWO-THE USER'S PROCESS) PAGE 1



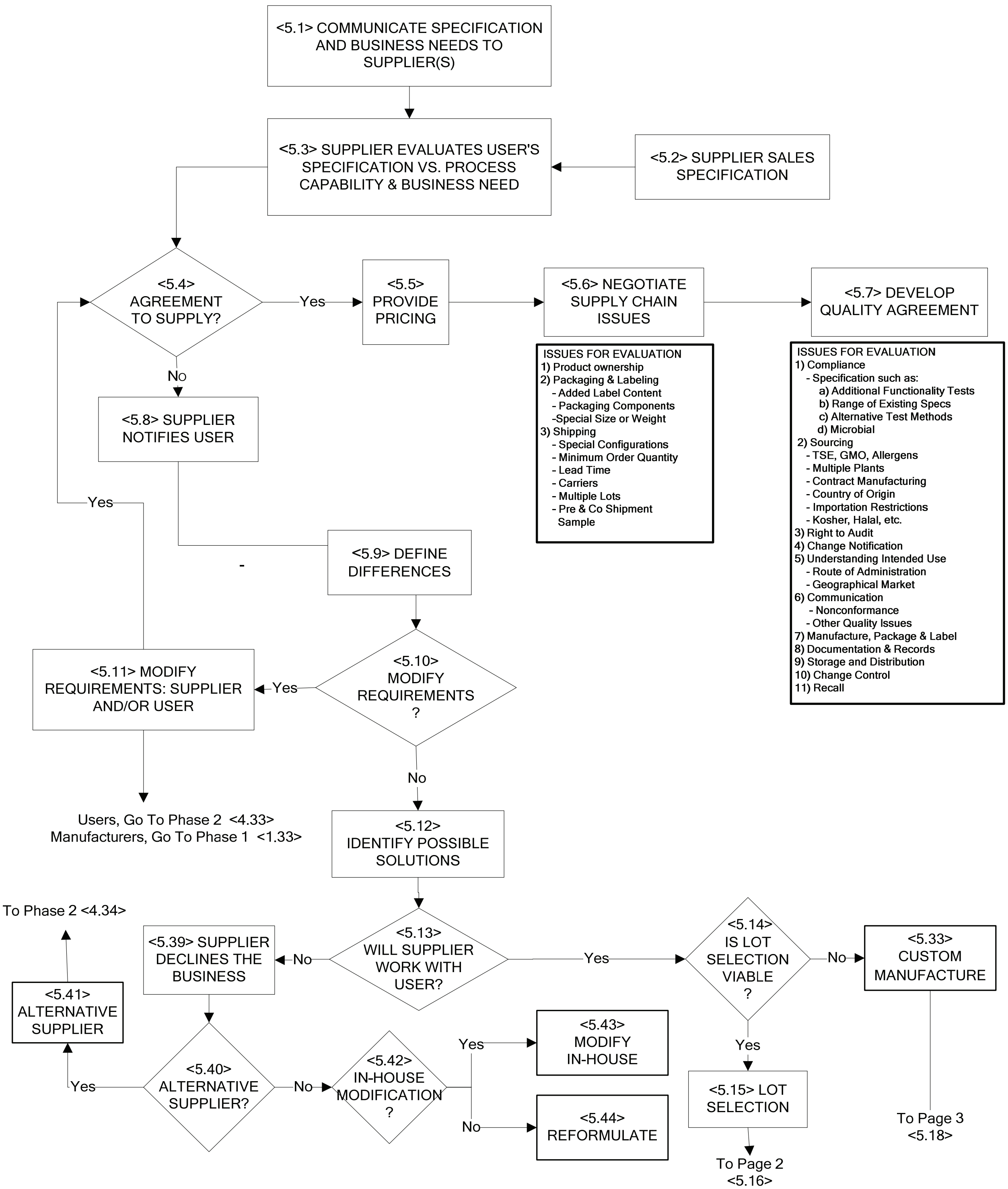
EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE TWO-THE USER'S PROCESS) PAGE 2



EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE TWO-THE USER'S PROCESS) PAGE 3

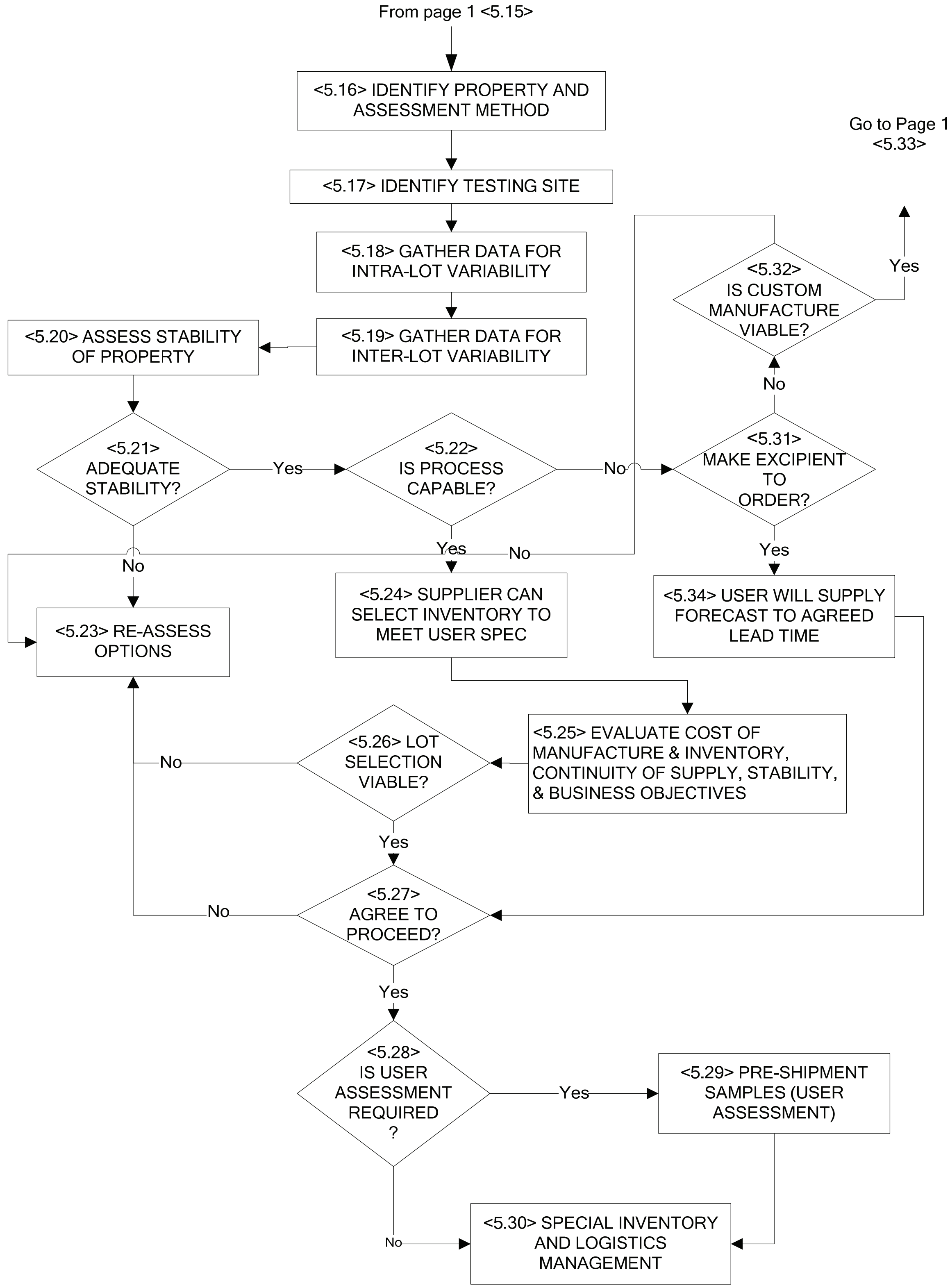


EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE THREE-THE NEGOTIATION PROCESS) PAGE 1



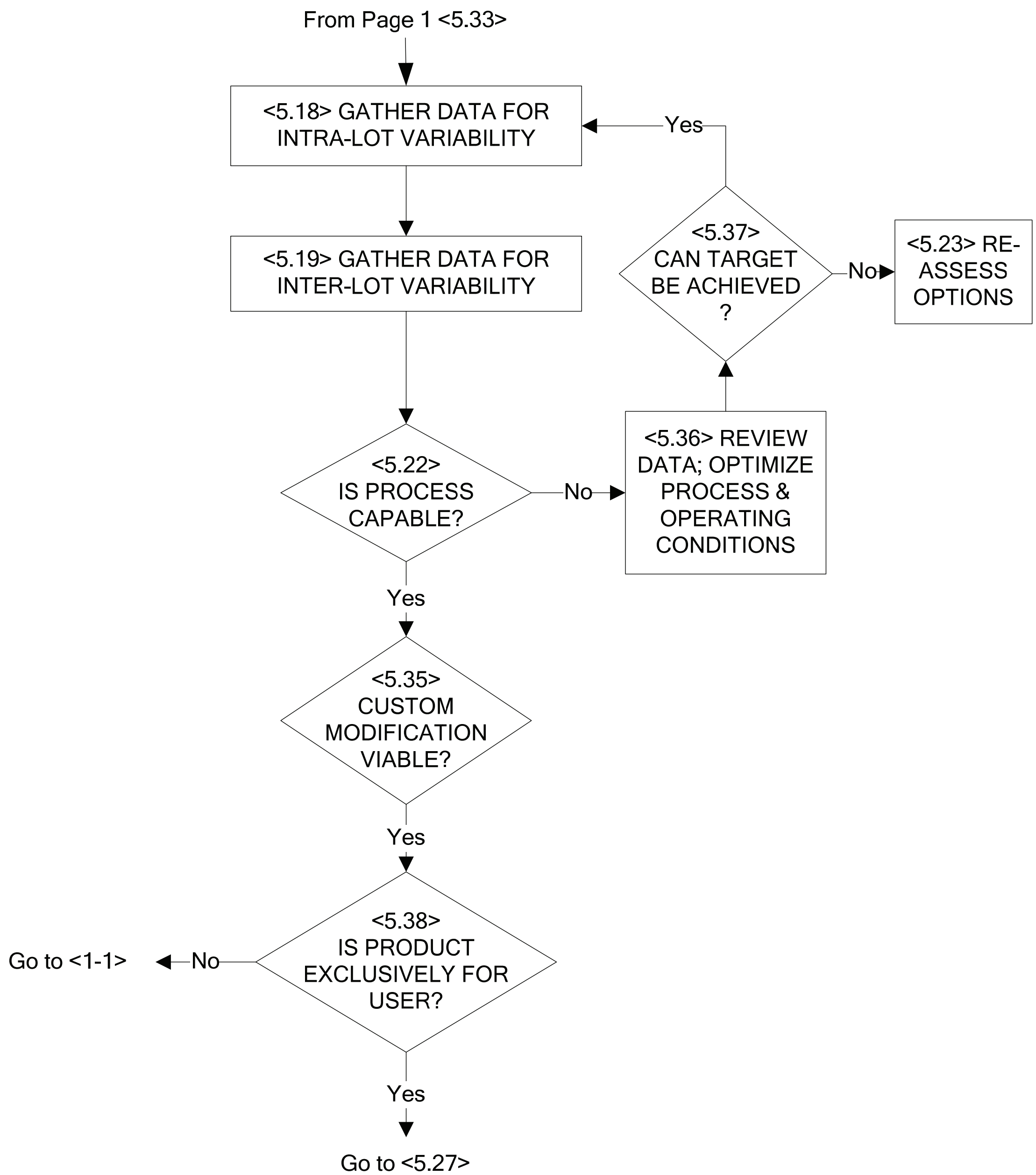
EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE THREE-THE NEGOTIATION PROCESS) PAGE 2

LOT SELECTION SECTION 5.4.1



EXCIPIENT DEVELOPMENT AND QUALIFICATION PROCESS
(PHASE THREE-THE NEGOTIATION PROCESS) Page 3

SUPPLIER CUSTOM MANUFACTURE
SECTION 5.5.3



APPENDIX B: DEFINITIONS AND GLOSSARY

Active Pharmaceutical Ingredient (API): Any substance or mixture of substances, intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body of man or animals.

Additive: A substance added to the excipient to improve or maintain a characteristic such as a preservative, flow agent, antimicrobial, etc.

Bill of Lading: A document used when shipping goods that describes the content of the shipment and accompanies it.

Certificate of Analysis: A document listing the test methods, specification and results of testing a representative sample from the batch to be delivered.

Certificate of Suitability to the European Pharmacopoeia (CEP): Certification granted to individual manufacturers by the European Directorate for the Quality of Medicines (EDQM) when a specific active ingredient or excipient is judged to be in conformity with a Ph.Eur. monograph.

Change Control: A process for management review of proposed changes that may impact the quality or regulatory conformance of the excipient.

Component: Any material present in the excipient that arises as a consequence of the raw materials and/or manufacturing process.

Composition Profile: A description of all of the components present in the excipient.

Concomitant Component: A material found in an excipient in addition to the major component(s) that is necessary for assuring the proper performance of the excipient in the drug formulation.

Contaminant: An undesired material of a chemical or microbiological nature or foreign matter introduced from a raw material, intermediate, or excipient during production, sampling, packaging, storage or transport.

Co-processing: Any mixture of compendial or non-compendial excipients that has been designed to be physically co-processed in a way which results in functional performance attributes when used in a drug application and which are not seen if the excipients are combined using simple mixing.

Customer Risk: The probability that a lot is released by the manufacturer although the product is nonconforming.

Date of Manufacture: A date indicating the completion of the final manufacturing process (as defined by the supplier for the particular excipient and process).

Design of Experiments: A series of planned experiments that uses statistical principles to select variable parameters with the objective of optimizing process performance.

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Document Control: The set of procedures to ensure documents can be identified as to their status e.g. draft, revised, approved, obsolete, superseded, etc.

Drug Master File (DMF): Detailed information about the manufacture of an excipient that can be submitted to the United States Food and Drug Administration, Health Canada, and the Japanese Pharmaceutical and Medical Devices Agency.

Endotoxin: A toxin that is produced within certain bacteria that is released only when the bacteria are destroyed.

Excipient: Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Expiry (Expiration) Date: The date designating the time during which the excipient is expected to remain within specifications and after which it should not be used.

Excipient Information Package (EIP): An IPEC initiative to provide standards for the exchange of data between excipient suppliers and excipient users. The EIP is comprised of the Site Quality Overview, Product Regulatory Datasheet, and Site and Supply Chain Security Overview. IPEC's Standardized Excipient Information Protocol User Guide provides information on the preparation of the EIP documents.

Expiration Period: The duration, normally expressed in months or years from the date of manufacture, within which the excipient can continue to be used.

Functionality: A desirable property of an excipient that aids and/or improves the manufacture, quality, or performance of the drug product.

Good Distribution Practices: The general principles of good practices in the pharmaceutical starting materials supply chain.

Good Manufacturing Practices: Requirements for the overall quality system under which drug products and their ingredients are manufactured, tested, and released. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For purposes of this guide, the terms GMP and cGMP are equivalent.

Impurity: A component of an excipient that is not intended to be present but arises as a consequence of the manufacturing process.

Inactive Ingredient Database: An FDA database containing information on excipients present in FDA-approved drug products.

Interchangeability: Functional equivalent in all respects to the original source material

Master Batch Record: Documentation of the steps necessary to produce a finished excipient by batch processing.

Master Process Flow: Documentation that describes excipient manufacture from raw material to final purification using continuous processing.

Master Process Log: Record of the operating conditions used for the manufacture of the excipient using continuous processing

Master Production Record: Record of the manufacture of the lot/batch of the excipient from raw material to completion.

Operating Characteristic (OC) Curve: A graphical technique for showing the performance of an accept/reject plan.

Other Components: Materials present in an excipient that arise as a consequence of the raw materials and/or manufacturing process and are not concomitant component.

Original Manufacturer: Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material.

Packaging Material: A material intended to protect an intermediate or excipient during storage and transport.

Pivotal Scale: A scale of cGMP pharmaceutical product manufacture less than full commercial scale but greater than $1/10^{th}$ commercial scale. Studies using such manufacture (e.g. product stability) may be used to support the marketing application.

Pre-formulation: Those studies preceding formal formulation design that are used to investigate the physical, chemical and biopharmaceutical properties of the API.

Process: The set of operating steps including synthesis, isolation, purification, packaging, etc. that produce the finished excipient.

Process Capability: Measurement of the process variability for a specified property.

Process Parameter: A measurable operating condition.

Process Step: A documented instruction to the excipient manufacturing personnel directing that an operation be done.

Process Validation: Documented evidence demonstrating assurance that a specific process will consistently produce excipient meeting its specifications and quality characteristics.

Processing Aid: A material added to a manufacturing step for the purpose of facilitating the completion of that step or subsequent step.

Producer Risk: The probability that a lot is rejected by the manufacturer although the product is conforming.

Production Specification: A list of tests, references to analytical procedures, and appropriate criteria for a material as manufactured.

Pyrogen-Free: A specification parameter stipulating the excipient is free of endoxin and any other fever causing agents.

Quality Agreement: A formal agreement between the excipient manufacturer and their pharmaceutical customer that stipulates the responsibilities of each party in meeting the regulatory requirements for sale and use of the excipient in a dosage form.

Quality by Design: The development of the design space, specifications, and manufacturing controls that result from pharmaceutical development studies using Design of Experiments, process analytical technology (PAT) and or prior knowledge.

Random Variation: Variation in the measured property whose distribution of results shows no predictable pattern.

Re-evaluation Interval: The duration, normally expressed in months or years, from the date of manufacture, throughout which the excipient should continue to conform to the specification and after which should be tested to confirm it continues to meet specification.

Retest Interval: (Re-evaluation Interval)

Sales Specification: A list of tests, references to analytical procedures, and appropriate criteria for a material as offered for sale.

Shelf Life: The length of time during which the excipient meets specification (see also expiration period, re-evaluation interval and retest interval).

Significant Change: Any change that alters an excipient physical or chemical property from the norm, or that is likely to alter the excipient performance in the dosage form.

Specification: A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material.

Statistical Control: A process that results in product that exhibits random variation of its property.

Sterile: Completely free from microorganisms such that, after inoculation of a suitable nutrient medium under aseptic conditions with the material, and followed by incubation at an appropriate temperature for 14 days, no growth of microorganisms is seen.

Supplier: Used here to denote the company providing the excipient ingredient to the pharmaceutical customer. May be either the excipient manufacturer or distributor.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Worst Case: A set of conditions encompassing processing limits, circumstances, equipment, etc., which pose the greatest chance of a failure in a process, to a product, or in a procedure, when compared to ideal conditions or those stipulated in a procedure. Such conditions do not necessarily induce product, process, or equipment failure.

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Printed in the USA by IPEC-Americas
1655 N. Ft. Myer Drive, Suite 700
Arlington, VA 22209